

NATIONAL INSTITUTES of HEALTH
NATIONAL INSTITUTE of CHILD HEALTH and HUMAN DEVELOPMENT

**Best Pharmaceuticals for Children Act
(BPCA)**

List Prioritization Review Panel

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VOLUME I

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1 P R O C E E D I N G S

2 [8:05 a.m.]

3 Welcome/Opening Remarks

4 Dr. Donald R. Mattison, NICHD

5 DR. MATTISON: We have two fairly long days in
6 front of us with a lot of discussion and action, so I
7 would like to begin, if we could.

8 I would like to take this opportunity to welcome
9 all of you from the NIH, and most especially NICHD. As
10 all of you know, this is the third exercise in which we
11 have looked at the drugs that are off-patent and tried to
12 identify the most compelling reasons or indications for
13 studying those drugs.

14 As we have had in the past, each of these
15 listening meetings has two general goals. The first is to
16 identify the indications and the drugs which you all will
17 deem are our highest priority.

18 The second encompasses a learning process for
19 the NIH and the FDA. Any thoughts that you might have
20 that would help us sharpen and improve our processes --
21 [off mic].

22 I would like to begin by thanking, especially,

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1 the experts we have here -- [off mic] and the materials
2 collected to help us through the first -- [off mic].

3 I would also like to thank members of the NIH
4 and FDA Steering Committee for their work on this, and
5 also notice the FDA for helping us as we discuss the
6 future of these drugs.

7 Finally, I would like to thank Tim for pulling
8 together this process this year, for putting together a
9 schedule and a set of activities, a more thoughtful
10 process -- [off mic].

11 Now I would like to turn the microphone over to
12 the FDA and Lisa Mathis, who is the acting director of the
13 Food and Drug Administration.

14 **U.S. Food and Drug Administration (FDA) Overview**

15 **Dr. Lisa L. Mathis, FDA**

16 DR. MATHIS: Good morning. I'm Lisa Mathis, the
17 acting director of FDA. First of all, I would like to
18 thank the experts for giving us your time and your
19 expertise, and also developing the list of priority drugs
20 that you have studied -- [off mic].

21 We have now a process through which -- [off mic]
22 that allows for the study of off-patent drugs. As you

1 know, today we will be making our priority list of off-
2 patent drugs.

3 [PowerPoint presentation.]

4 DR. MATHIS: As you can see up here, what we are
5 going to be doing today is making the priority list, but I
6 wanted to give you some idea of what happens with this
7 priority list once you guys are done with it.

8 The next step is that the FDA will issue a
9 written request. Now, a written request is basically a
10 written agreement where we list the minimum requirements
11 that we want from the study in order to appropriately
12 label drugs. We initially issue that written request to
13 both AMDA and MPA [ph] holders of the drugs, so off-patent
14 and on-patent manufacturers of the drugs.

15 They have 30 days to tell us whether or not they
16 agree to do the study. If they agree to do the studies,
17 then industry pays for those studies. However, if they
18 decline, then we go ahead and refer those written requests
19 to NIH.

20 Just some more detail about what happens is
21 that, once you guys give us the list, we go through that
22 list and select the drugs in order to go ahead and start

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1 issuing the written request. We talk to different FDA
2 review divisions, and we also get input from NIH and
3 NICHD.

4 We put together a literature review, look at the
5 labels, obtain safety data and news data, and then we go
6 ahead and talk again with the review divisions and the
7 appropriate institutes at NIH as well as NICHD, and then
8 we write a draft written request.

9 Once that draft is put together, we go through a
10 pretty extensive process with NIH as well as with the FDA.

11 We go to a pre-PDX where we talk internally, and then we
12 go to the PDX group, which is the pharmacologists group
13 that look at both the PK and PD sections of the study.
14 Then we go to PDX, which is actually cross-divisional. We
15 have pharmacists, project managers, statisticians, and we
16 all look at the written requests to make sure that it's
17 both consistent and appropriate.

18 Then we go ahead and issue the written request
19 to the holders, as I discussed before, and if they agree
20 to do it, they do it. If not, we give it to NIH, and NIH
21 goes through the process of putting it in their contract.

22 This is just the process that we go through, a

1 timeline for development of the written request. As you
2 can see, once we have the list that you all will produce
3 today, we go through a pretty extensive timeline in order
4 to get those written requests issued. Then once they are
5 issued, again, NIH has to go through an extensive process
6 to issue the contract.

7 Now, what happens once the clinical studies are
8 completed is still theoretical at this point. However,
9 what we would like to do is that the final study reports
10 are submitted to both the NIH and FDA and then submitted
11 to public docket. We look at them and review them,
12 remembering that all pediatric submissions in response to
13 written requests have a six-month review clock.

14 Then we will go ahead and draft it into labeling
15 and negotiate with the sponsors, as well as putting it
16 into the public record, probably through the Federal
17 Register.

18 Now, today, we are asking you to provide us with
19 your judgment regarding the value of finding and
20 conducting additional studies of the specific drugs that
21 are on the somewhat final list, and then also to help us
22 with scientific questions that need to be addressed

1 regarding the drugs and the indication in the pediatric
2 population, as well as identifying gaps in the labeling.
3 So that way, we do the right studies to get these drugs
4 labeled for pediatrics.

5 We do have a website, if you want to contact the
6 FDA in the future. This is our contact information, and
7 also, that is where our link is. Then this is our contact
8 information as well.

9 I would like to finish up by really thanking all
10 the experts again for showing up to give us your common
11 expertise. This means a great deal to FDA. I would also
12 like to thank my colleagues at the NIH and FDA for showing
13 up and really providing us with a lot of support and
14 effort.

15 Now, we are going to start with Dr. Lasky
16 talking about prioritizing the drugs.

17 **Prioritization Overview**

18 **Dr. Tamar Lasky, NICHD**

19 DR. LASKY: I wasn't going to thank anybody
20 until the two days were over, but I was going to thank
21 everybody for coming, and then after the two days, see.

22 [PowerPoint presentation.]

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1 DR. LASKY: Don actually summarized what I was
2 going to say, but he did it so well and he did it very
3 briefly. Still, I would like to go over some of the
4 details. I think everyone is familiar, but I think it is
5 also useful to go over some of the details of what led to
6 the process as it is now.

7 As you will all know, BPCA mandates that NICHD,
8 in consultation with FDA, develop this list on an annual
9 basis. He mentioned that this is our third year. These
10 are the drugs that we have already listed.

11 We have learned a lot each year, and we expect
12 to continue learning. This year, when we set out to plan
13 the process, we set three goals: one, which was to improve
14 the documentation and written record, because as this
15 grows and becomes more recognized, we know that people
16 will want to look into the process and understand the
17 process.

18 One of our goals was to expand the range of
19 expertise and input from the public, and the third major
20 goal was to expand the knowledge base and adapt this
21 process as we expand the knowledge base.

22 I see we also made another really big change,

1 and this kind of was less deliberate and less conscious,
2 but in our work with FDA as we learned about the written
3 request process, we learned that when FDA issues a written
4 request, they generally link a drug to an indication. As
5 we worked on the written requests and worked on developing
6 the contracts, we saw it was useful to know what
7 indication we were talking about when talking about the
8 drugs.

9 So we are shifting over from previous years
10 where we would talk about a drug in a general manner to
11 trying to specify the indications that we are talking
12 about. A person's opinion would be very different from
13 one indication compared to another, and this really rests
14 on our experience.

15 As I went over preparations for today's meeting,
16 I realized it is a bigger shift than we probably realized
17 at the time, but it is going to change a little bit the
18 nature of our conversation and thinking.

19 Some of the process highlights. As you know, we
20 have an annual List Development Working Group. I'm the
21 chair of the working group. We have participants from
22 NICHD and from FDA, and we have been meeting close to

1 monthly, or at least have monthly phone calls talking
2 about when we can't meet that month.

3 We have incorporated input from FDA on a
4 constant basis, as well as from the NIH institutes and
5 Centers for Disease Control and Prevention, and from a
6 wide range of professional organizations.

7 Another feature that we added this year was
8 publication of a preliminary list in the summer. This
9 year, it was in August 2004. There were 23 drugs, and it
10 is available for public comment; we haven't caused much of
11 a stir.

12 Another feature was the move to having the
13 meeting in October instead of December and to have it be a
14 two-day meeting and have it be expanded to scientific
15 considerations of the kind of studies we would like to do.

16 So prioritization and thinking about the kind of
17 scientific questions.

18 In the process this year, we referred closely to
19 the legislation, which lists these four points on how we
20 prioritize drugs. They are not very specific. We haven't
21 gone beyond it, but they do leave room for us to develop
22 our thinking further.

1 Points A and B address the issue of availability
2 of information. Point C talks about whether we think
3 these studies are going to have an impact on health of the
4 pediatric population. Neither of these are defined
5 further.

6 The fourth one is whether reformulation is
7 necessary. That is kind of a different criteria that we
8 haven't incorporated as closely, either.

9 So in operationalizing availability of
10 information, we began this year with a pilot study
11 approach with the company Metaworks, and they did an
12 assessment of the count of abstracts for each of 64 drugs
13 and the type of study design, the topic, and the age
14 groups.

15 What we wanted to do with this availability
16 information is operationalize it in a way where we could
17 have systematic assessments, systematic literature
18 reviews, and eventually lead to meta-analysis.

19 In our pilot study, this is the type of output
20 that we receive. I think this is the drug Quinidine. You
21 can see if you go across the top, it was broken down by
22 indication, and as we go down, you will see where the

1 studies took place. You can see what kinds of studies
2 they are, the age groups studied, and the outcomes of
3 focus in the study.

4 This will help us in evaluating the literature,
5 because we could take an indication and look up or down
6 and see whether that indication has been studied in a
7 particular age group, and then come to some kind of
8 quantitative assessment of whether we consider this
9 adequate or not. It is not a rigid criteria, because you
10 can have 10 lousy RCTs compared to two excellent RCTs, but
11 just having these quantify what the literature is.

12 Our marker for availability in this kind of
13 quick and dirty first cut was whether there were 10 or
14 more randomized clinical trials in the literature since
15 1990. Again, it is not a rigid criteria.

16 We did come up with some interesting findings
17 which we hope to get out into published literature as well
18 for the 64 drugs. They were broken down by the number of
19 studies, and you can see that most of the drugs had very
20 few studies. Twenty-five only had one to five RCTs, but
21 there are a few drugs that had an enormous amount of RCTs
22 published in the literature since 1990, in particular,

1 Amoxicillin, Quinidine, Dexamethasone, Epinephrine,
2 Methotrexate, and Prednisolone.

3 Our thinking was, there is such an abundance of
4 literature, it may all be inferior quality, but it
5 certainly needs to be looked at before we would say
6 equivocally that the literature is inadequate. These
7 drugs will be reviewed intensively by the contractors who
8 are going to be working on systematic review, and they
9 will go beyond looking at abstracts but do systematic
10 literature reviews and, if possibly, meta-analyses.

11 The other criteria that we put a lot into was
12 the issue of frequency of use, basically how many kids use
13 the drugs. There are many more ways to quantify this
14 issue. We can start thinking about dose and duration, but
15 in the beginning we want to know just how many kids are we
16 talking about.

17 We had a very nice relationship with Express
18 Scripts Data. They did this for us on a voluntary basis,
19 which is great. They did it quickly and promptly, and
20 then said they had no time to continue it. So we got what
21 we got. They are a pharmacy benefits management company
22 with 30 million covered members in 50 states. This was

1 from 2002; 380,000 were continuously enrolled. They gave
2 us data on 941 unique or combination products.

3 The way we conceptualized it is to think about
4 the prevalence curve, 100 continuously eligible children.

5 Again, for the future, we would want to know about
6 children who are not necessarily continuously eligible,
7 but as a first cut, these were the data we got.

8 What we found is, I think, again, very, very
9 interesting. Unlike the adult population where we could
10 say 45 percent of adults are on a daily medication, most
11 children are not on medication. Very few children take
12 medication. The highest frequency was for very few drugs,
13 which was over 10 percent of the kids getting that drug in
14 a particular year.

15 We ended up stratifying the frequencies on
16 orders of magnitude, going over six orders of magnitude,
17 and then grouping the top four orders of magnitude, which
18 is a very big spread quantitatively, from greater than one
19 in 10,000 all the way up to greater than one in 10. This
20 was concerned high frequency, and we considered low
21 frequency the lower two amounts, which are the less than
22 one in 10,000 and greater than one in a million.

1 Then we have the zero category, where we either
2 did not have data, or it is used on an inpatient basis, or
3 it is not used at all.

4 We applied these numbers to a list of off-patent
5 drugs. Sixty-four of them were high frequency. Remember
6 that high frequency is over four orders of magnitude.
7 Thirty-nine were low frequency, and 97 were without
8 frequency of use information. We have a long way to go in
9 getting more comprehensive data.

10 We conducted an outreach last January or
11 February, and we gave people until the end of April to
12 respond to this list of drugs and the frequency
13 information. We sent the mailing to about 150
14 professional organizations, as well as to our NIH sister
15 institutes and to FDA and to CDC.

16 We did not suggest an indication but asked
17 respondents to specify the indications they felt were of
18 concern.

19 I think the responses were from a little more
20 than 90 organizations. There are binders on the table,
21 about six, with copies of the responses. These are some
22 of the organizations that responded.

1 We had a separate MPA input which recommended 56
2 new drugs for further study. We ranked the input from all
3 these different sources, giving one point to each
4 recommendation and five points to the FDA recommendations
5 because, as you know, FDA has really worked on this and
6 brings a special level of expertise to this issue.

7 This is the distribution of rankings for the
8 approximately 200 drugs. For some reason, there were two
9 drugs that people took the time to write in and say we
10 should look at them, so we gave them negative one point.
11 These would go in the zero category. Most drugs are in
12 the zero or one category. That is, very few people
13 thought they were of critical importance.

14 We used the cut-off of three or above, because
15 that gave us a group of 70 drugs. This shows the low. We
16 had 225 drugs in February. There was a lot of movement in
17 and out of this group of drugs. Drugs go back on patent.

18 That is something we didn't know about. They
19 are granted exclusivity or are discontinued. So we have
20 to take them off the list for consideration in the off-
21 patent process, then drugs rise to the surface.

22 An interested group will recess tomorrow. It is

1 a group of dermatological drugs which were added in April.

2 They have always been off-patent, but they have been
3 added in response to FDA hearings last fall about safety
4 issues. So we will be discussing it tomorrow.

5 In the end, we had 70 drugs that were ranked
6 three or higher. I just wanted to let you know that we
7 did not follow the frequency of use information, blindly.

8 We considered it, but we did not let it dictate whether a
9 group was considered.

10 Nonetheless, we had 20 of the drugs with no
11 information on frequency of use. Thirteen had a low
12 level, less than one in 10,000 kids using it per year.
13 Thirty-seven were drugs where frequency of use was greater
14 than one in 10,000 per year, so it is kind of a nice
15 distribution.

16 In moving from the 70 to 23, it was not as
17 mathematical as, probably, we would all like to see it.
18 We sat together and talked about it, and we realized that
19 if we did it mathematically, we would have 19 dermatologic
20 drugs in the final group. We didn't want that. We didn't
21 think that would serve any of the purposes, and we tried
22 to distribute the shortages in each of the groups that

1 were present.

2 We also tried to honor the input from, in
3 particular, NIH institutes, Centers for Disease Control,
4 as well as the other organizations that really voluntarily
5 took the time to write in their comments. Some of them
6 were quite lengthy and quite helpful.

7 NIH, for example. We received responses from
8 the National Institute for Mental Health, and they
9 suggested Citalopram and Clonidine. It turns out that
10 Citalopram was either granted exclusivity or back on-
11 patent. Something happened there.

12 NHLBI had nominated Azithromycin and Cefuroxime,
13 both in children with sickle cell disease. Azithromycin
14 is already on our list twice for different indications
15 and, you know, there may be a time when we bring it on
16 again for this particular indication, but we ended up just
17 going with one of them.

18 So it is not a straight mathematical process.
19 Here is a good example of how we used the frequency data
20 as well as our other criteria. It only received a ranking
21 of three, but it is a very high frequency drug. There
22 were one in 100,000 kids using it in a given year. That

1 is not high frequency. I tried to remember -- no, it is
2 still in our high frequency group.

3 It stayed off patent. It is off-patent and
4 hasn't been granted exclusivity. It hasn't been
5 discontinued.

6 The Metaworks review found 19 randomized
7 clinical trials since 1990 for any indication, but it
8 found zero in patients with sickle cell anemia. So while
9 there is literature about this drug, there isn't a
10 literature about this drug in this indication. We could
11 comfortably say that we felt the literature was not
12 adequate for this indication.

13 The charge for today and tomorrow, as has been
14 said, is we are going to be looking at 23 off-patent
15 drugs. We are also going to look at four on-patent drugs
16 which go through a different process and get not fully
17 developed. The drugs were referred by FDA, the foundation
18 for NIH, and from the NICHD.

19 Our charge, which has been said already:
20 whether we study this drug and indication and what are the
21 scientific questions that need to be addressed.

22 The format, which is approximately the primary

1 review of a talk, summarizes pertinent comments for
2 approximately 10 minutes. The secondary review will add
3 some comments.

4 Our FDA colleagues are here, medical officers
5 from all the divisions, and they will have an opportunity
6 to speak for five minutes or so, and there will be about
7 10 minutes for discussion.

8 Dr. Bob Ward, professor of pediatrics at the
9 University of Utah, has graciously agreed to be chair of
10 this panel. He will let you know when you have around one
11 minute.

12 I did want to say, when you see a green light,
13 you have two minutes. When you see a yellow light, you
14 have 30 seconds. When you see a red light, time is up.

15 Now, over to Bob.

16 **Review 3: Off-Patent Drugs**

17 **Dr. Robert Ward, Moderator**

18 DR. WARD: I think there is actually very little
19 to add to what has been said. Our charge is to rank these
20 drugs and evaluate them on behalf of children so that we
21 can, at the end of the day, create a list of drugs that we
22 feel will be of most benefit to children based on their

1 study.

2 As many of you in this room know -- I see Dr.
3 Blumer over at the corner -- there is a limited amount of
4 funds available for these studies, so our task is not a
5 small one. We don't have limitless funds, and so they
6 have to be spent wisely. I think we have to balance what
7 we think is the most important for children and also what
8 is feasible for children.

9 With that, we will go ahead and get started on
10 the review process. Let me just mention, there are some
11 representatives from industry here. What I would ask
12 would be that if you are from industry, to speak with the
13 individual person on the panel who is reviewing your
14 particular medication. We are going to try to not make
15 this an open-ended discussion that could occur around a
16 specific proprietary product.

17 With that, let's start with Ethambutol.

18 Dr. Wiederman.

19 **Review of Ethambutol**

20 **Dr. Bernhard Wiederman**

21 DR. WIEDERMAN: Thanks. Good morning. Don't
22 worry; I just have a short presentation. I did want to

1 put some of my thoughts down.

2 [PowerPoint presentation.]

3 DR. WIEDERMAN: What I was hoping I had there, I
4 was thrilled to see that Metaworks had gone through and
5 done all this summary in relation to all these drugs, and
6 a few days later, I realized they hadn't done that process
7 with Ethambutol.

8 But in the packet, a product of the FDA, was
9 actually, I think, 39 studies dealing with Ethambutol,
10 which was very helpful. I looked around for a few more.
11 I just wanted to summarize a few things.

12 This is obviously a drug that has been around
13 for a long time, since the 1960s. There are studies
14 documenting increasing frequency of use of Ethambutol in
15 pediatric tuberculosis. This is mostly driven by emerging
16 drug resistance in TB, so Ethambutol is often the fourth
17 drug added for a child with TB but suspicion or in an area
18 of high drug resistance.

19 I think going through the studies -- I won't
20 spend a lot of time on that -- there are a lot of data on
21 efficacy of regimens using Ethambutol for treatment. It
22 is very responsive to tuberculosis in children. It is

1 possible to pull out enough from those studies, if there
2 is enough detail, to make an efficacy claim. An FDA-
3 approved efficacy claim, I'm not sure. It takes some work
4 to pull some of that out.

5 I did want to focus just briefly on the main
6 sticking point of using Ethambutol in children, and that
7 is the ocular side effects. The most serious side effect
8 in patients who are given Ethambutol is primarily
9 retrobulbar optic neuritis, which usually is related,
10 usually irreversible, and, at least at lower doses, is
11 most uncommon and perhaps rare. But because of the
12 difficulty at a particular age in testing visual fields
13 and color vision in young children, it has caused some
14 concern for using this drug in children.

15 This is just one of the early studies that shows
16 essentially a little bit of the dose-related effect of
17 this. You can see very high doses are not used anymore
18 for extended periods of time; there are only six patients.

19 Two of them in this study of patients in Chicago
20 developed visual side effects for what we would now call a
21 higher range dose, about 5 percent of patients. At a
22 little bit lower dose, nine out of 200. These are all

1 adult patients.

2 When you look through some of the studies of the
3 treatment of TB and try to tease out children in those
4 studies and how well or not so well they were followed for
5 ocular problems, there are sort of three types of studies.

6 This is from the Medical Research Council of the U.K.
7 The study was done in Korea.

8 One is where there is more formal or active
9 follow-up for visual problems. So we did a lot of tests
10 on these kids who were included in there. It was unclear
11 in this study, as it is in most studies, of what they do
12 with the very young children in terms of some of the tests
13 they were measuring or using here wouldn't have been
14 possible in very young children because you need
15 cooperation. They mentioned 27 children under five years
16 of age who received Ethambutol -- [off mic] have any
17 problems detected.

18 This is a more typical study in terms of ocular
19 toxicity, where the authors were clearly aware of a
20 potential problem, but they just commented that nobody
21 complained about visual problems. There was apparently no
22 formal surveillance for ocular problems. This kind of

1 passive surveillance is the majority of studies.

2 This may be the only study where a group of
3 individuals in India measured visual-invoked responses in
4 children three to 13 years of age, and 47 children, again,
5 with -- [off mic] all had normal studies.

6 There is one nice literature review, apparently
7 recently, that really combined all the studies -- [off
8 mic] with the better, more active follow-up. There were,
9 combining all six studies, it ends up being 343 children.

10 There was one possible ocular toxicity case, although the
11 study that mentioned this doesn't go into a lot of detail.

12 This author commented that at the usual dosage,
13 which is equal to a dosage of 15 milligrams per kilogram
14 per day, the effects are rare, and advocated for going
15 ahead and using Ethambutol in young children. Obviously,
16 just that one author's opinion.

17 In terms of filling out my score sheet, for the
18 Task 1 score sheet, I came up with a score of four. Of
19 the three drugs that I was assigned to be primary or
20 secondary reviewer, this was the lowest score of my three
21 drugs. This happens to be the drug I think would be most
22 important of those three drugs to stay on the list.

1 I think the scoring system is actually quite
2 good, but I think what is missing and why I think
3 Ethambutol might have a little higher importance than the
4 score would predict, is because of more of the
5 epidemiology and type of problem that pediatric
6 tuberculosis represents. I think emerging resistance
7 means we are going to be pushed to do this more and more
8 to get a lot of drugs available.

9 No. 2, unfortunately, young children with TB are
10 similar to canaries in coal mines. So when you see a
11 young child with active tuberculosis, it usually
12 represents recent infection from somebody who is spreading
13 it throughout the community, as opposed to reactivation
14 disease that doesn't become a problem until the adolescent
15 age group. So from that ideologic standpoint, pediatric
16 tuberculosis is important.

17 As I indicated, I think there may be enough
18 efficacy data out there. If someone could go through and
19 piece out the results of these larger studies, although
20 many of them are in other countries, not the U.S.

21 I think what would be important to focus on are
22 the ocular toxicity problems, to include both better

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1 follow-up studies, not necessarily randomized trials but
2 just in everyday treatment settings, but also some studies
3 perhaps using visual-invoked responses in younger children
4 and infants who at least get some level of security.
5 Still, this is a known side effect of the drug and it
6 certainly will happen in children.

7 That's all I have.

8 DR. WARD: Thank you very much.

9 Dr. Overturf.

10 **Secondary Review of Ethambutol**

11 **Dr. Gary D. Overturf**

12 DR. OVERTURF: I just have a couple of points.
13 I agree that the major issue is ophthalmic toxicity. To
14 my knowledge, really, there has not really been a well
15 confirmed single case of toxicity in children; that is,
16 ophthalmic toxicity.

17 The problem is just as has been stated, that a
18 lot of the studies have not really looked at this closely,
19 or they have been conducted in developing countries where
20 there has been virtually technology to do so.

21 The other thing is that this has become a more
22 important drug in recent years because of the emerging

1 resistance. In 1990, the World Health Organization
2 estimated there were about 1.3 million new cases of
3 tuberculosis in children in that single year, and there
4 are about 450,000 deaths in children.

5 That is exceeded only by one other really common
6 infectious disease that we see in the non-developed world,
7 and that is actually measles. Obviously, malaria has a
8 major impact in those countries as well.

9 The other thing is that the annual incidence of
10 tuberculosis in children increased from 40 percent from
11 1985 and to 1993, and especially is high in minority
12 populations. So that, if you look at the non-childhood
13 population, the increase in tuberculosis during that time
14 was only about 13 percent. So the rates in children have
15 tripled and increased, and much of that has been due to
16 resistance, which has developed primarily in HIV-infected
17 individuals.

18 Actually, Ethambutol is recommended not only as
19 a single drug but often as a combination drug to replace
20 one of the two primary drugs when there is resistance. So
21 it has become a more important drug, again, to know
22 exactly what its safety is for children, because it

1 becomes an important issue.

2 Now, it also has been affected by resistance,
3 and resistance in most studies now of Ethambutol, it can
4 be as high as 5 to 10 percent, so that along with its
5 resistance.

6 So I agree with most of the comments. I think
7 the major issues are safety with this drug. The PK and PD
8 data are pretty well known with this drug.

9 There is one additional comment, and that is
10 that it may have major importance in children because
11 children suffer disproportionately from the complications
12 of CNS disease in tuberculosis, and this has very good CNS
13 pharmacology. It is one of the unique drugs. It is not
14 as good as Rifampin and INH, but it has very uniquely good
15 pharmacology. That has been well studied in the past, but
16 not in children, again, not as to its pharmacology.

17 So my score was a little higher. I gave it a
18 seven, and that was the highest score that I had given any
19 drug. So I generally agreed with the comments.

20 Thank you.

21 DR. WARD: Thank you.

22 FDA Review Officers Krause and Meyer, any

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1 comments?

2 **FDA Review of Ethambutol**

3 **Dr. Carl N. Kraus**

4 DR. KRAUS: Carl Kraus, FDA reviewer. My only
5 comment might be more of a pragmatic one. Having reviewed
6 some of the utilization data for Ethambutol in the United
7 States, it seems as though there is little to any use of
8 Ethambutol in children in the U.S. Of course, this was a
9 cursory review.

10 I'm not sure if other folks around the table
11 have more information on the number of pediatric cases
12 seen in this country, but that being the case, it seems
13 even if it were to be evaluated, it would be difficult at
14 best to try and conduct a safe review of sufficiently
15 large to be robust enough that it would provide evidence
16 of safety in kids.

17 Secondly, there are alternates means of
18 evaluating safety from data overseas. There are 505(b)(2)
19 evaluations that have been conducted recently. There is
20 one in which there has been 20 or 30 years of use
21 internationally of a drug, which points to a probable,
22 reasonable safety profile. Ethambutol, too, has been used

1 for more than three decades overseas.

2 I haven't had a chance to look at the literature
3 overall, but my guess is there may be some ways of
4 compiling all the data and seeing if these are ways to
5 look at this.

6 **Open Discussion**

7 DR. WARD: It looks like we have a discrepancy
8 between your data about use and our Infectious Disease
9 colleague's experience here.

10 Gary.

11 DR. OVERTURF: I would agree that it is probably
12 not used a lot in the United States, but this is one of
13 those issues -- and I agree with the comments that were
14 made -- that is primarily of worldwide use. It probably
15 is used a great deal in other countries, because it is a
16 less expensive drug, it can be given orally, and
17 tuberculosis is obviously more common.

18 DR. ZAOUTIS: You know, the published
19 literature, including that article by Leff and Leff [ph],
20 which they had done a series of surveying public health
21 clinics, did point to an increase and suggested, I
22 believe, about a quarter of kids being treated for TB in

1 these settings were receiving a combination of contained
2 Ethambutol. So I'm not sure if there are different
3 databases or what exactly. I can only comment anecdotally
4 that, certainly in my practice in D.C., it is very common
5 to put children on Ethambutol.

6 DR. LASKY: I was going to make a comment on the
7 frequency of use data that our Express Scripts data set
8 did not have information about it, but this was a data set
9 that looked at commercially insured children. My sense is
10 that when we look at the Medicaid data and the uninsured
11 data, we will find differences.

12 The other option we ought to look at is, at some
13 point we will have data on prevalence or physician visits
14 for tuberculosis, and we really need to know the
15 underlying condition here rather than whether Ethambutol
16 is used. I'm not sure that we have that yet.

17 DR. WARD: My experience has been that you are
18 only as good as your database, and when it is a database
19 almost of convenience, it really will depend on who their
20 population is. If it is commercial, it is really not
21 going to capture --

22 PARTICIPANT: I would suspect, even children

1 with insurance will get their TB drugs through the local
2 health department, so an Express Scripts, I think, will
3 not pick it up. But the information ought to be
4 available.

5 DR. WARD: Other discussion?

6 Yes.

7 DR. GROGG: Yes, a couple comments. I would
8 like to see it available in a suspension form, if that is
9 possible, for pediatric patients. I know it can be mixed
10 at the present time, but suspension form would be nice.

11 Understanding all the comments that have been
12 made, we have seen a lot of resistance of tuberculosis
13 coming to the United States with a lot of foreign travel
14 coming into the United States. It would be nice to have
15 this drug available for those resistant strains.

16 DR. WARD: Jeff.

17 DR. BLUMER: Just a word of caution. I think
18 the point about safety is indeed the most important.
19 Assessing safety in the context of other drugs, which is
20 the only way that this is used, is truly a challenge, and
21 I think we have to keep in mind, whether we would be able
22 to effectively generate data that would be useful in

1 labeling in the context of varying regimens for anti-
2 tuberculins therapy is difficult, although things that may
3 be satisfactory for us as clinicians may not be
4 satisfactory.

5 I would like to hear the FDA reviewers' response
6 to that in terms of what the yard stick might be to get
7 safety data people will label when you are using a drug
8 like this in varied contexts.

9 DR. KRAUS: I completely agree. I think that
10 the cleaner data sets probably are the older ones where
11 there weren't four drug regimens available to patients.
12 Again, I have not had a chance to look back and see what
13 exactly is available in the literature, but I think in
14 doing so there may be some reasonable amounts of data.

15 DR. WARD: Let me ask our Infectious Disease
16 consultants before we go on, are there four drug regimens
17 that could include Ethambutol and an alternate fourth drug
18 without ocular side effects as a comparator?

19 DR. ZAOUTIS: Well, usually the choice we are up
20 against is that fourth drug being either Ethambutol or an
21 aminoglycoside, Streptomycin or Kanamycin. So that is
22 where we are, and obviously, we would prefer Ethambutol,

1 but with a concern. But there are other possibilities.

2 DR. OVERTURF: I thought the question was
3 specifically whether there were other drugs that were
4 thought to have the same toxicity, and I don't think there
5 are. This is a unique toxicity to this drug in all
6 tuberculosis combinations that I know of.

7 DR. ZAOUTIS: I think the only problem would be
8 if you included patients with TB meningitis, who get
9 cortical blindness, optic atrophy, and all those. That
10 would be a very difficult population to look at for this
11 toxicity, but aside from CNS disease --

12 DR. KRAUS: Currently, the CDC recommends a
13 four-drug regimen for everyone in the United States
14 because of the more than 4 percent drug resistance rates
15 in the United States. If that were the case, you don't
16 get your census back for at least six weeks afterwards
17 with your cultures. I'm not sure how you could conduct a
18 reasonable study. I mean, it is difficult.

19 DR. ZITO: Non-Infectious Disease addressing.
20 I'm wondering if it would be useful to know a little bit
21 about what proportion of children's needs are not being
22 met by the current options so that you get a sense of what

1 the size of the benefitted population might be. In other
2 words, is every child who would come in become a
3 candidate.

4 DR. ZAOUTIS: I don't think the kids' needs are
5 being met. We are just plowing ahead and giving it
6 regardless. I think the issue is, have we created some
7 visual problems down the road that we are not hearing
8 about. My sense is that it can't be very common or we
9 would be hearing about it. It is sort of an unknown.

10 DR. WARD: It is the CD recommendation, though,
11 at this point for drug therapy for children, or is that
12 dependent upon identification of resistance?

13 DR. OVERTURF: Well, the organism is nearly
14 always not acquired from a child. It is usually acquired
15 from the contact. So there are really three situations.
16 There is a situation in which the child is known to be
17 exposed to an individual and they earn susceptibility from
18 that individual.

19 There is the rare situation where we acquire the
20 organism from a child, and actually, with modern
21 microbiology, organisms are grown and sensitivities are
22 available much earlier than they used to be, but they are

1 still somewhat lengthy.

2 Then there is the third situation, where we
3 don't have an index case and we don't have an isolate from
4 the child. In those situations where we know of
5 resistance or we suspect resistance because of the
6 potential origin of the infection, then Ethambutol is
7 frequently used as one of the combinations.

8 Sometimes aminoglycosides are used as well, and
9 a lot of times aminoglycosides are used in some
10 jurisdictions because people are concerned about the
11 current label, which does not allow the drug to be used in
12 children less than 13 years old, or does not recommend its
13 use.

14 DR. WARD: I was going to ask for a
15 clarification. Okay.

16 DR. OVERTURF: So it is not recommended for use
17 under 13 years.

18 DR. WARD: Okay. Yes.

19 DR. SNODGRASS: Just a brief comment. How would
20 one specifically measure ocular toxicity in a one-year-old
21 or two-year-old? I mean, I guess you would have to have
22 some sort of an agreed-upon definition.

1 DR. WARD: I think it is the date at BER.

2 DR. SNODGRASS: You are going to be limited to
3 that. In other words, will that pick up more subtle
4 defects?

5 DR. OVERTURF: No, it doesn't, because the early
6 problem is really color distortion and other kinds of
7 problems, which really can't be picked up by those
8 technologies, to my knowledge.

9 DR. WARD: So it would reach a point of
10 established damage to be picked up by BER, okay.

11 Other comments, discussions?

12 [No response.]

13 DR. WARD: You have in front of you a blue sheet
14 for which you need to put your score for the experts on
15 the panel, and those will be collected at the end of the
16 day.

17 Let's move on to Flecainide for arrhythmias.

18 Dr. Stiles.

19 **Review of Flecainide**

20 **Dr. Alan D. Stiles**

21 DR. STILES: Flecainide is an anti-arrhythmia.
22 It is used primarily in treatment for -- [off mic].

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1 Having reviewed the information that came with
2 this, I actually scored this a five, and in general found
3 several issues that I thought were of particular
4 importance in considering in discussions.

5 One is that there are limited bits of
6 information available about the oncology of this
7 particular drug in very young children, that being the
8 zero- to six-year-old group.

9 Secondly, most of the studies used it in
10 conjunction with other drugs and after other drugs had
11 been used, and it is very difficult to glean from the
12 literature any information on whether there are actually
13 interactions between those drugs and what those were.

14 Thirdly, this is used with existent arrhythmias,
15 so your patient situation is very atypical. Although in
16 the adult literature, where this drug is primarily steady,
17 it is known that ventricular dysfunction is a major
18 problem, some of the children, particularly the young
19 ones, actually have significant amounts of ventricular
20 dysfunction left over from either in utero events or a
21 period of time where issues have led to the treatment of
22 the dysfunction.

1 Having said that, in the literature there are no
2 reports of pro-arrhythmic activity in children, which was
3 of some interest and, I think, an issue that is important
4 to consider following.

5 So to summarize what I think are the issues to
6 put on the table, one is the interaction with other drugs,
7 and the second is actually whether or not there is enough
8 information to intelligently dose this drug using the
9 dosing schedule and so on that we are aware of.

10 The one caveat is that -- [off mic] very small
11 children will compare -- [off mic] of the drug orally, and
12 that may make some difference to dosing that may lead to
13 an unusual situation.

14 DR. WARD: Thank you.

15 Steve, do you want to speak from the podium or
16 there?

17 Dr. Lawless.

18 **Secondary Review of Flecainide**

19 **Dr. Stephen T. Lawless**

20 DR. LAWLESS: I actually gave it a higher score,
21 a seven, the high of four. What struck me was the
22 utilization number of Flecainide. I was actually, to use

1 a technical term, blown away by the relative usage of
2 it for the indication it was there for.

3 It should be for intractable arrhythmias.
4 Utilization looked more like what I would have expected
5 for something like Lidocaine or an oral drug or something
6 for the same thing. So it tells me that the usage out
7 there is being used a lot more commonly for kids who
8 probably aren't really good candidates for it. So there
9 is that side effect there.

10 The indication for it is to prevent ventricular
11 arrhythmias and sudden death. The main side effect is
12 sudden death, even though the side effect is rare. So
13 that scared me. I think this is a relatively dangerous
14 drug used for a selected indication, which is probably
15 being over-used. So that is why I gave it the higher
16 score.

17 DR. WARD: Would either of you comment, or maybe
18 someone in the audience here, about its pathway of
19 metabolism with respect to drug-drug interactions? I
20 confess I'm not familiar with what its pathways of
21 metabolism are. Or, do we know?

22 DR. STILES: I think as far as what is

1 available, at least in the papers that I looked through,
2 there is some information about its excretion. Largely,
3 it is in the kidney, a little bit of change in the liver.

4 But beyond that you are getting beyond my level of
5 expertise to comment.

6 DR. WARD: Let me ask the FDA review officers if
7 they would like to make some comments. If not, that is
8 fine. This is the opportunity.

9 **FDA Review of Flecainide**

10 **Dr. Susan McCune**

11 DR. McCUNE: I'm Susan McCune, and I'm in the
12 Pediatrics Division. I'm also a neonatologist, so I'm
13 much more comfortable in the neonatal period.

14 Just a couple of comments about the label.
15 While it is not labeled specifically as an indication for
16 pediatric use and it does say that safety and efficacy in
17 the fetus, infant, or child have not been established in
18 double-blind randomized placebo control trials, there is a
19 fair amount of information about the metabolism PK
20 information, even in the newborn up through the
21 adolescent.

22 There is dosage information provided in the

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1 label as well. It specifically stated that it should be
2 undertaken under the care of a pediatric cardiologist.

3 There was a question, I believe, about the
4 safety information. There are some reports in the
5 literature about the co-arrhythmic events. The question
6 is how severe they are. There is a wide spectrum of
7 severity associated with it.

8 **Open Discussion**

9 DR. LAWLESS: Yes. The one thing that struck me
10 is that, even though you had the incidence of the
11 outpatient prescriptions, is that my guess would be that
12 the drug is primarily used in kids who have congenital
13 heart disease who have been repaired and are on this
14 because afterwards their heart is irritable and they are
15 put on something. So that is where the outpatient
16 prescriptions come in.

17 But if you look at the dosage PK and
18 information, there is a lot of variability there. So the
19 idea of the highest-risk kids, probably my guess would be
20 if you looked at distribution, would be the lowest-ages
21 kids and how long you stay on it. So that is also, I
22 think, a high reason for it to be studied.

1 DR. McCUNE: That is correct. In addition, it
2 is not the first-line drug that would be used, and
3 obviously, with the concerns about safety, but in some
4 kids, this is the only thing that is available.

5 DR. LAWLESS: Right. And they are on Digoxin,
6 most of them. My guess would be for the period of time
7 that the effect of Digoxin and Flecainide, there may be
8 kind of an interaction or a combination effect. It is a
9 little bit uncertain territory.

10 DR. WARD: Also, I think that there is
11 significant use of this drug in patient lives that never
12 reaches an outpatient environment. Probably, the children
13 at greatest risk are the ones who have been given this
14 drug on the inpatient side, not the outpatient side. We
15 have no utilization information as far as I'm aware with
16 that.

17 Do you use this for infant SVT?

18 DR. BLUMER: We have used it for infants with
19 refractory SVT, and I think that the problem with this, as
20 I see it -- and I agree with what Steven said, but I think
21 that we will run into a problem in trying to assess this.

22 I think that the information on the label, if you look at

1 least in the published literature that supports it, is a
2 hodgepodge. People have done pharmacokinetic studies of
3 convenience so that patients who happen to be exposed and
4 some of them happen to get some levels, and the doses that
5 are recommended are doses that have been used, not doses
6 that have been studied, and that creates difficulty.

7 On the other hand, in the context of use, if it
8 were to be studied in the context of its current use, we
9 would be doing this with the next millennium by the time
10 patients get to that point.

11 So I think if we are going to consider
12 recommending it, if it is a viable tool, and it appears to
13 be, you may have to do it, in some ways, the way
14 antibiotics are studied, and that is, take children with
15 SVT and actually use it as a first-line drug to get that
16 critical data about pharmacokinetic safety, exposure, and
17 efficacy, and then put it in its context. That creates a
18 problem when you have this unknown pro-arrhythmic effect
19 there.

20 So I just think in terms of identifying need, we
21 have to identify the feasibility of potential cautions
22 that have to be exercised in moving forward.

1 DR. WARD: That would be a tough consent form,
2 wouldn't it.

3 DR. LASKY: I just want to ask FDA again, this
4 was a drug suggested by FDA? So I just wanted to make
5 sure you got all your points across about why we need this
6 study.

7 DR. WARD: It is the old Tommy Smothers "Take
8 it."

9 [Laughter.]

10 PARTICIPANT: I would definitely defer to Dr.
11 Mattison.

12 [Laughter.]

13 DR. LAWLESS: I have a question, then, on the
14 recommendation for study to the point that Dr. Blumer just
15 said.

16 This drug is primarily -- my guess would be a
17 lot of it would be started in hospital.

18 DR. WARD: Right.

19 DR. LAWLESS: Would the recommendation for study
20 be something that has to be started in hospital and then
21 proceed on? I mean, I would think if therapy were started
22 in the outpatient.

1 DR. WARD: It would seem to me that in that type
2 of a design and that clinical situation in which you have
3 refractory SVT, one of the questions would be, is it just
4 SVT, what does your electrophysiology actually show you.
5 But you would start it with careful monitoring, but the
6 pro-arrhythmic effect may be months down the road. At
7 least in the adults, it has been relatively random, it
8 seemed to me, when it occurred.

9 Any other comments?

10 DR. HIGGINS: I would like to add that the
11 Cardio-Renal Division actually thought that it wasn't
12 properly labeled according to the current usage, which
13 would be starting as an inpatient and then going over to
14 oral outpatient therapy. So, basically, the review
15 division had looked at it and looked at the data in
16 labeling and, you know, tried to assess whether or not
17 that really reflected actual use.

18 DR. BLUMER: In terms of trying to answer your
19 initial question, there are polymorphisms in its
20 clearance. I don't remember what they are, but it is a
21 drug that always appears on one of those lists. That does
22 confound us, so there will be those complications as well.

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1 DR. WARD: Any other discussion?

2 [No response.]

3 DR. WARD: Thank you.

4 We have been joined by Dr. Duane Alexander,
5 director of NICHD, who wants to make some remarks about
6 the whole process we are about today.

7 **Comments**

8 **Dr. Duane F. Alexander, Director, NICHD**

9 DR. D. ALEXANDER: Good morning, everyone, and
10 thank you for fitting me in. I promise not to take much
11 of your valuable time. You have many more important
12 things to do today rather than just listen to me, but I
13 did want to say a special thanks to all of you for joining
14 and participating in this very important process.

15 When the Congress passed the Pharmaceuticals
16 Procurement Legislation, it assigned to NICHD the
17 responsibility for the very first step in that whole
18 process, which is identifying and prioritizing the list of
19 drugs for study.

20 This is extremely important because there are
21 far more than can be studied. There are \$25 million
22 available each year for these studies. While that sounds

1 like a lot of money, when you get to actually funding
2 costs of the studies that are involved, it doesn't go very
3 far. So the prioritization process is extremely
4 important.

5 We have been working together in partnership
6 with the Food and Drug Administration on this process and
7 have done it several different ways. The first year, we
8 were in a hurry. There wasn't time to do very much.

9 So what we did was rely on wise people. We
10 pulled together wise people. We gave them a list of all
11 the off-patent drugs and said, "Which of these are the
12 most important to study?" It is actually a little easier
13 when you are picking the first ones. It gets a little
14 harder each time you go, each round, but they did an
15 excellent job of selecting off that list the most
16 important ones just based on their general knowledge and
17 information.

18 But that can't go on forever. We were lucky the
19 first time. We did very well, a pretty good job, I think,
20 of it, but as you go on with the second and then the third
21 lists, the process needs to become more sophisticated.

22 Our staff during the course of the last year has

1 devoted a major effort to trying to make this process as
2 scientifically based and as information-based as possible,
3 so that rather than just top-of-the-head knowledge and
4 experiential use as a guide, we now are making efforts to
5 provide information to you and the future groups that will
6 be engaged in this process of priority-setting with
7 additional information to go on: what is the extended
8 use; what is the information in the literature that is
9 available about usage and metabolism of these drugs; what
10 is the need perceived in the community by actual survey
11 and query from practitioners and their perception of these
12 for further information and actual labeling of drugs for
13 their use.

14 So this process is getting more sophisticated.
15 This is far and away the most sophisticated one that we
16 have had, and we are committed to making this process even
17 better each succeeding year as we go about it.

18 So you are quite an entity with an extremely
19 important role, and working for your colleagues in
20 practice on providing us with information about which are
21 the most important drugs for us to study, given the
22 limited resources that we have, to get information for

1 pediatric labeling that will help guide their practice and
2 help protect children who are receiving these drugs.

3 So thank you for doing it. We are committed to
4 making the best effort we can to provide information.

5 At the end of the day tomorrow, we would hope
6 that you would give us your suggestions for what might
7 make this process even better for you as participants, and
8 for other participants in the next year, because there is
9 going to be a next year and a next year. Any additional
10 information that you would find useful before you came to
11 this meeting to help you make a judgment and provide the
12 guidance that we depend on so much.

13 So any thoughts that you have as you participate
14 in this process about what else might be helpful to you in
15 providing the information that we seek.

16 So thanks to all of you for participating. We
17 appreciate and value it very much. We hope that you find
18 this process useful and can also give us guidance in how
19 we can make it even better. Thank you very much.

20 DR. WARD: Thank you, Duane.

21 I just want to emphasize exactly what is said.
22 This has been a process in evolution, and input and

1 feedback will be terribly important in refining it for
2 next year. This is far and away the best organized
3 approach to this, providing a comprehensive review of
4 literature on a CD to make it convenient for you to
5 review. I think that has enhanced it.

6 So other aspects that can be improved would be
7 useful to the process and useful to make it serve children
8 better.

9 Dr. Tom Green was to talk about Chlorothiazide
10 for hypertension.

11 **Review of Chlorothiazide**

12 **Dr. Thomas P. Green**

13 DR. GREEN: Chlorothiazide is a diuretic that
14 has been used for a long time in children and in adults.
15 It acts by blocking electrolyte reabsorption in the renal
16 tubule, primarily in the distal renal tubule. For that
17 reason, it has a whole lot of indications and use in
18 disorders of fluid electrolyte imbalance, particularly
19 those of edema.

20 The indication that we are asked to look at this
21 for is in hypertension, and in fact, the mechanism of
22 action in the treatment of hypertension is a little less

1 well defined. It probably is in part related to its
2 actions in the renal tubule, but it may have other actions
3 as well.

4 The formulation for Chlorothiazide that we have
5 been asked to look at are the labeling for Chlorothiazide
6 is for the intravenous administration, and we can talk
7 about that. I think, given the order that we are in, we
8 are going to talk about Hydrochlorothiazide next, and I
9 think there is a balance of indications that we will see
10 in Chlorothiazide and Hydrochlorothiazide.

11 Fortunately, it appears that the therapeutic
12 index for Chlorothiazide is fairly wide. Therefore, the
13 problems with its use tend to be related to the drug
14 mechanism of action. In other words, imbalances of food
15 and electrolytes.

16 For children, the use of Chlorothiazide is
17 related to hypertension in its use, although I think
18 Hydrochlorothiazide is much more widely used. It is used
19 in the newborn period for hypocalcemia, where there are
20 disorders of electrolyte imbalance and fluid disorders
21 where loop diuretics and other more highly effective
22 diuretics are used. Hypocalcemia tends to be a

1 complication of loop diuretics, like Furosemide. The
2 Thiazides have the offsetting benefit of decreasing
3 urinary calcium excretion and thereby reversing or
4 preventing the calcium deposition, the nephrolithiasis and
5 so forth, that is seen with loop diuretics.

6 For those indications, it is fairly widely used,
7 although I don't have good data on how widely used that
8 is. I think that might vary from center to center.
9 However, there are not good alternatives for the Thiazides
10 in that hypocalcemic indication.

11 The labeling of Chlorothiazide precludes or does
12 not encourage the use in children. There are no specific
13 data provided in order to guide the use in children on the
14 label.

15 The currently available information is really
16 quite sparse. The literature that was provided in the
17 review here actually kind of indicates, I think, how poor
18 the literature is on Chlorothiazide. In fact, most of the
19 articles that were included were for Hydrochlorothiazide
20 and not specifically for Chlorothiazide.

21 I think I only found six of the articles that
22 dealt specifically with information relative to

1 Chlorothiazide in any indication, and those were by and
2 large case reports and reports in combination with other
3 agents. So really a dearth of literature that is
4 currently available.

5 As I mentioned earlier, I think the drug is
6 thought to have -- I hate to kind of extrapolate too far
7 when I just said there is not much data about it, and then
8 reassure you that the efficacy and the safety is good, but
9 I think the impression is that the therapeutic index is
10 wide. Nonetheless, it would be, I think, fair to say that
11 the information available for children is sparse, and the
12 quality of information is not great.

13 I think that that leads to kind of a paradox in
14 trying to assess the value of getting further information.

15 If the drug is not widely used, used for only a few
16 indications, and thought to have a wide therapeutic index
17 without significant toxicities that would directly relate
18 it to what you know to be the mechanism of action, it is
19 not clear to me that the benefit of prioritizing this
20 particular drug for further study would be high.

21 DR. WARD: Steve?

22 **Secondary Review of Chlorothiazide**

Dr. Stephen T. Lawless

DR. LAWLESS: Echoing what Tom has said, I think the idea of the use of the drug, the two major side effects are the electrolyte problems, especially the sodium and potassium stuff, because these kids are usually on it for a long period of time. That is usually a bigger problem.

The other thing is the confusion a lot of times between Hydrochlorothiazide and Chlorothiazide, so people mistaking one versus the other.

DR. WARD: It is only a twenty-fold difference.

DR. LAWLESS: That's right.

[Laughter.]

DR. LAWLESS: The other thing, actually, is it is used more abundantly and used for hypertension in the acute setting. Its use in renal failure actually is a contraindication. It is not that well known or well appreciated that it can actually cause renal failure or worsen renal failure, as opposed to other diuretics, so a little caution that way. But, really, Tom, it generally has a wide therapeutic index. It is not a big deal.

The other thing, with the tendency now with the

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1 guidelines for hypertension to be more strict, people are
2 going to be looking for drugs which just have a mild
3 effect, to get the systolic from like a 120 to a 118 type
4 of a thing. So the use of this may go up only because you
5 don't want to use a big gun just to drop a pressure just a
6 little bit in a six-year-old.

7 So there may be that balance there, but it
8 usually tends to be safer. I did rank it lower in terms
9 of not a high priority because it is safer that way.

10 DR. WARD: Dr. Grylack?

11 **FDA Review of Chlorothiazide**

12 **Dr. Laurence Grylack**

13 DR. GRYLACK: Thank you. Larry Grylack,
14 Division of Pediatric Drug Development.

15 I generally agree with the comments made. I
16 would raise a general issue, though, and certainly this is
17 something the Division of Pediatrics feels strongly about,
18 namely that with any of the anti-hypertensives that are
19 being studied, that adequate long-term follow-up studies
20 be done specifically looking at growth and development.

21 As you all know, in the literature during the
22 last year, there have been some useful studies recognizing

1 the fact that there are some neurodevelopmental sequelae
2 from hypertension itself, so it will be important in
3 studies of hypertensives to try to distinguish the effects
4 of medication from the effects of the disease itself.

5 Secondly, I raise the question to the experts on
6 the panel as to whether both Thiazides need to be studied
7 at this time, whether they are both priorities. I know
8 that Dr. Green had made some comments about distinguishing
9 the indications and the priority for Chlorothiazide and
10 Hydrochlorothiazide, so that would be another issue that I
11 would want to mention.

12 Finally, of course, being a neonatologist, I
13 have to make some remarks about the newborn. Certainly,
14 protein binding for these compounds is variable, and
15 certainly that has to be taken into consideration in
16 looking at issues such as jaundice in the newborn.

17 So those are my remarks.

18 DR. WARD: Dr. Pursley?

19 **FDA Review of Chlorothiazide**

20 **Dr. DeWayne M. Pursley**

21 DR. PURSLEY: For full disclosure, my name is
22 DeWayne. I'm also a neonatologist.

1 DR. WARD: And neonatology is well represented
2 around the table here.

3 [Laughter.]

4 DR. PURSLEY: I would comment that I would
5 hazard a guess that the use of Chlorothiazide is actually
6 quite prevalent among neonatal intensive care units around
7 the country and probably not for this indication. I don't
8 recall that I have ever used a diuretic as an anti-
9 hypertensive in an acute setting. However, it is used
10 quite commonly for babies with bronchopulmonary dysplasia.

11 In fact, it is probably one of the most common
12 medications which we discharge infants with chronic lung
13 disease.

14 I think that the experience in Boston, at least
15 in this case, is similar to the experiences of other NICUs
16 around the country. We are using it quite a bit in our
17 NICUs.

18 DR. GRYLACK: I agree, and certainly in our
19 discussions prior to this meeting, we were talking about
20 its use in BPD, but alas, the indication is hypertension
21 so we couldn't get our teeth into the BPD issue.

22 **Open Discussion**

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1 DR. WARD: Jeff.

2 DR. BLUMER: I think that both Thiazides raise
3 an interesting paradox here. First of all, I think
4 despite the increase in utilization and really
5 thoughtfulness about the use of Thiazides in adult
6 patients with hypertension, I think I want to echo what
7 was said. We virtually have no experience using Thiazides
8 for hypertension in children. When we use Thiazides, it
9 is as a diuretic.

10 So the whole issue of pharmacokinetics,
11 pharmacodynamics, and whether these are effective as
12 hypertensives for the kids that we see with hypertension
13 remains open. I think that that underscores the potential
14 importance here of looking at one or the other of these
15 drugs.

16 I think the other issue is that with the
17 questions that are raised by Thiazides and the large
18 utilization of them in the neonatal intensive care unit
19 and as an adjunct to loop diuretics, it probably does need
20 to be considered.

21 So I think this is an area that I would suggest
22 we don't just put aside, but I do think in terms of

1 siloing the indications we probably need to think about
2 them and then look at them again.

3 DR. WARD: Tom, would you comment on the
4 calcium-spearing action in the neonate? Do we really have
5 data that demonstrate that?

6 DR. GREEN: I hate to make a comment with all
7 the neonatologists in the room because I'm not one of
8 them.

9 [Laughter.]

10 DR. GREEN: But my impression is -- please
11 comment -- that it looks like there is adequate data on
12 prevention or even resolution of calcinosis and calcium
13 excretion when Thiazide is used either alone or in
14 combination with loop diuretics.

15 So, please, any comments?

16 DR. LAWLESS: Yes. I mean, I did one year in a
17 nephrology fellowship, so I'm half-representative of that.

18 [Laughter.]

19 DR. WARD: You are the collecting duct.

20 DR. LASKY: Just one kidney.

21 DR. LAWLESS: One kidney, that's right.

22 [Laughter.]

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1 DR. LAWLESS: We actually never used Thiazides
2 for the hypocalcemic effect -- I mean, the calcium-
3 spearing effect in the kidneys. I forget the Thiazide
4 that was used, but it was not Chlorothiazide per se.
5 There was a third type of Thiazide, but I forget the name
6 of it. It wasn't as strong of a calcium-spearing effect.
7 So if you have somebody with hypocalcemia, Chlorothiazide
8 actually wouldn't be the Thiazide you would go to.

9 DR. GREEN: Well, I could just ask the
10 neonatologists here, especially when we are dealing with
11 prioritizing drugs and only being able to choose some of
12 the indications here, my impression -- again, this is
13 doing a reality check here -- is that the value of
14 Chlorothiazide as opposed to Hydrochlorothiazide is it has
15 an intravenous formulation.

16 So, in the period when you are still using IVs
17 and so forth you have Chlorothiazide, but when you are
18 switching to an oral agent, are you using
19 Hydrochlorothiazide exclusively, or is there a reason to
20 choose another Thiazide other than Hydrochlorothiazide
21 when going for the longer term oral outpatient use?

22 PARTICIPANT: We would virtually always switch

1 to Hydrochlorothiazide, but I couldn't agree more, we
2 would never use this for its anti-hypertensive effect.

3 DR. WARD: How does that impact our task here
4 today, in that it was labeled for hypertension?

5 PARTICIPANT: I was going to come around to
6 that. I was going to transfer the response to that aspect
7 to Dr. Mathis and Dr. Mattison here and let them discuss
8 that.

9 DR. MATHIS: I think if you look back to our
10 first list that came out, you will see a significant
11 number of anti-diuretics for BPD. In response to this,
12 NICHD and FDA really developed a working group spearheaded
13 by Dr. Giacoia that looked at this indication.

14 One of the problems that we have is just the
15 problem of studying BPD: how do we define it; how do we
16 define improvement. So part of the problem with
17 developing drugs for this indication is the lack of
18 clarity in defining this indication and improvement in
19 this indication. That is probably something that we are
20 going to need to address prior to being able to develop
21 drugs for that indication, but we would like to look at
22 them ultimately because we do know that that is a primary

1 use.

2 DR. WARD: I think that Chlorothiazide has
3 reached this list with this indication based on the
4 extrapolation from adults almost purely.

5 DR. MATHIS: Let me just remind people, we have
6 these booklets. These were sent out to people beforehand.

7 The American Heart Association suggested
8 Hydrochlorothiazide occasionally used as a diuretic in
9 CHF. They have about eight drugs. It is a one-page
10 comment, so we don't have more information.

11 One of the things I think we could do in the
12 coming years if we don't feel satisfied here, is ask
13 people to provide more information. That is not very much
14 to go on.

15 Also, the American Society of Pediatric
16 Nephrology included Chlorothiazide in its list. They have
17 listed quite a few drugs, so they wouldn't have helped us
18 prioritize. They listed about 30 drugs to look at, but
19 just to keep this in mind that there were many paths to
20 get to this list.

21 PARTICIPANT: The other thing, if either Alan
22 Shapiro or Dr. Rodriguez would like to comment on some of

1 the Thiazides, too, for hypertension?

2 DR. WARD: Could I defer that? Let's go ahead
3 and discuss the Hydrochlorothiazide, and then we will keep
4 this discussion on both, since they really are
5 representative of the same class.

6 Go ahead and do Hydrochlorothiazide.

7 **Review 3: Off-Patent Drugs (continued)**

8 **Review of Hydrochlorothiazide**

9 **Dr. Thomas P. Green**

10 DR. GREEN: Ditto for what I said about
11 everything else about Chlorothiazide. Again, the
12 indication that is listed here is Hydrochlorothiazide for
13 hypertension. The mechanism is expected to be virtually
14 identical to that of Chlorothiazide. It is only available
15 in an oral formulation.

16 As contrasted with Chlorothiazide, there is a
17 reasonable literature in the recent literature and the
18 data that was sent along on Hydrochlorothiazide, I think
19 representing its more widespread use for several
20 indications.

21 It is used as an adjunctive therapy in the
22 treatment of hypertension, and it is used somewhat, I

1 think, without a lot of data in the literature about the
2 same indications that we talked about before for
3 generalized disorders of edema causing the naturally
4 diuretic effects.

5 However, a lot of the literature that has been
6 around for the last 10 years deals with the use of
7 Hydrochlorothiazide for a number of other disorders in
8 which, in my view, the thinking about this, the value of
9 further study of this drug, would carry over to a lot of
10 other and essentially orphan indications.

11 Disorders that lead to increased calcium
12 excretion in the urine, such as renal hypophosphatemia and
13 other genetic disorders that lead to hypocalcemia, are
14 pretty widely treated with Hydrochlorothiazide and used
15 for a long period of time and used beginning in early
16 childhood.

17 In addition, disorders of nephrogenic diabetes
18 insipidus where not dealing with a calcium excretion
19 caused some changes in the renal handling of salt and
20 water and thereby improved patients' long-term water
21 balance, and have been shown to improve their long-term
22 growth and general health.

1 So while those are really orphan indications
2 affecting a very small number of patients,
3 Hydrochlorothiazide is used in those several circumstances
4 and I think therefore has wide impact.

5 Probably back on task, I think the real reason
6 we are asked to look at Hydrochlorothiazide has to do with
7 its use in the more common disorders. I guess no
8 additional comments, or I will carry over the comments
9 that I made about Chlorothiazide in terms of the rather
10 paucity of studies in children. On the other hand, the
11 perception of relatively wide therapeutic index and
12 safety, except for the direct knowable disorders of
13 deranged fluid and electrolyte imbalance.

14 So here, I would rate it somewhat higher,
15 probably more -- and maybe this is not legitimate in terms
16 of our task -- but more on the kind of carryover value of
17 the knowledge to many other children with a variety of
18 disorders for which there otherwise wouldn't be therapy.

19 DR. WARD: Thank you.

20 DR. STILES: Yes.

21 Alan, do you want to provide secondary review?

22 **Secondary Review of Hydrochlorothiazide**

Dr. Alan D. Stiles

DR. STILES: Not a neonatologist comment this time. I think the other really important reason to consider this drug around anti-hypertensity cases is the obesity epidemic. We are clearly beginning to use this drug very frequently on multiple age children, where before, that was unlikely to be an indication that would be pulled out. As it is in adults, it is the first-line anti-hypertensive often pulled out of the hat with these children who have also type II diabetes and other issues.

So in my opinion, that raises this to a much higher level of concern, taking everything else. There is a gigantic literature here about calcium excretion and other things. There is not much literature about the use of this drug as an anti-hypertensity control.

DR. WARD: Actually, Larry, do you want to go ahead and comment from the FDA? I want to hear about the frequency of use for hypertension and obesity.

FDA Review of Hydrochlorothiazide**Dr. John Alexander**

DR. J. ALEXANDER: I think it was an excellent comment. We definitely need to be aware of that. Just a

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1 few additional comments.

2 As far as the literature with regard to HCTZ, it
3 has been used or studied in combination with other drugs.

4 So that is something we can be aware of in terms of
5 usage.

6 Secondly, as far as the calcemia issue, one
7 reassuring study I came across was that although it did
8 decrease the calcium excretion in the urine, it did not
9 decrease bone mineral density in non-ambulatory children.

10 This was a group of children with mild malignancy. So
11 that is reassuring in terms a positive sense in terms of
12 its usage.

13 Also, in terms of other drug interactions, if it
14 is used concurrently with Dopamine in certainly critically
15 ill patients, it may in fact increase the diuretic effect
16 of the Dopamine, or vice versa. Dopamine might affect the
17 diuretic effect of the Hydrochlorothiazide. So needless
18 to say, there are a number of drug interaction issues that
19 will need to be taken into consideration.

20 It is mentioned in the fourth report as being
21 one of the drugs being considered for usage in
22 hypertensive children.

FDA Review of Hydrochlorothiazide**Dr. Alan M. Shapiro**

DR. SHAPIRO: I'm Dr. Alan Shapiro. I'm from the Division of Pediatric Drug Development. I'm also one of these people with one kidney. I'm primarily an infectious disease specialist, but I have also spend some time in pediatric nephrology in some training.

I wanted to echo Dr. Stiles' comments about the use of the Thiazides. Right now, at this point, most of the drugs that have been studied for hypertension in children have been the newer drugs, which have been namely the ASE inhibitors. Yet the older category of drugs, as we know in the adults, have a lot of efficacy, and it is considered first-line.

When you look at the Joint National Committee Report No. 7, they pick out Thiazides as being the first choice or first line for someone who has what we would say stage one hypertension, which the fourth report has also treated with the same category in kids.

We are seeing larger amounts of hypertension due to the obesity and due other causes that we are not completely aware of, and I think the point about studying

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1 these drugs, and specifically the Thiazides, we need to
2 know what are good agents to work with these kids.

3 All the studies that have been done with anti-
4 hypertensives look at the blood pressure lowering over a
5 short period of time. We have no clue about the clinical
6 end effects of putting kids on anti-hypertensives for a
7 long period of time, whether it is going to change their
8 cardiac damage, kidney, retinal disease, a lot of the
9 things we think we see in adults.

10 Yet we also don't have any clue, looking at the
11 hypertension versus the treatment, whether there are long-
12 term effects on growth and development.

13 So I would be one in support of putting the
14 Thiazides higher up on priority, because we need to know
15 this information.

16 **Open Discussion**

17 DR. LAWLESS: I think that if you link this,
18 part of the study is a link towards an obesity management
19 program and it is part of the obesity management --
20 obesity is going to be a major national priority -- then,
21 yes, you have to get the dosing of what is the effective
22 dose to use. You can't base it on weight in obese kids

1 for the long term. You just can't do that.

2 If it is not linked to that, if there are going
3 to be recommendations for obesity management and this is
4 going to be out there, you have to study it. You have to
5 link it together and not leave it open. If it is not
6 going to be done, you can still have it a lower priority.

7 DR. SHAPIRO: I looked over this fourth report
8 quite well, and I know that they have a stage management
9 for the kids with pre-hypertension, those with stage one,
10 and those with stage 2, which essentially very closely
11 parallel what is in the adults. For a kid who has stage
12 two hypertension, they are put on anti-hypertensives.

13 Like I said, we are still running into the fact
14 we don't know these anti-hypertensives very well, and we
15 are just picking what we are familiar, because the ASE
16 inhibitors were newer. You could apply exclusivity to
17 them and they could get a benefit for study. The older
18 drugs do not have that benefit, and that is where we come
19 in.

20 DR. WARD: Yes.

21 DR. KARKOWSKY: There are two issues I would
22 like to raise. The first issue is that diuretics are a

1 very effective drug in adults for African Americans, in
2 contradistinction to the ASE NARBs, which are not
3 particularly good. Depending upon your target population.
4 that might be a useful reason to increase the priority.

5 Second of all, the appreciation for the dose of
6 the diuretic has markedly changed over the last decade.
7 People were overdosed in the past, and the toxicity was
8 markedly increased because of that. Even if you know that
9 the drug does work, does anybody have any idea what dose
10 to use in kids, okay. Is it worth that amount of work to
11 better define what is a cheap and useful drug in a
12 population that might need it.

13 DR. WARD: Other comments?

14 Yes.

15 DR. ZITO: I just was going to offer the
16 observation that if one were to look at the history of
17 Thiazides over the last 30 years, there probably has been
18 a significantly greater utilization of
19 Hydrochlorothiazide, which would argue then that the
20 safety database would be significantly better for that
21 drug than the other. It might help make the case for it.

22 DR. SNODGRASS: Yes, a couple of short comments.

1 One is, if there were an IV formulation of
2 Hydrochlorothiazide, would you have any reason to use
3 Chlorothiazide? Just something to think about.

4 The other is, with the dose issue, there is data
5 from adults that six months after stopping
6 Hydrochlorothiazide in adults, you still have an anti-
7 hypertension effect the precapillary arterial resistance
8 sites. So there are a lot of unanswered issues about
9 those long-term effects.

10 DR. GROGG: From the general pediatric side of
11 things, I would like to recognize Dr. George Giacoia. He
12 has been one of my mentors in the past. George, good to
13 see you.

14 From general pediatrics, really, do we utilize
15 Hydrochlorothiazide for hypertension, because it is almost
16 always used for hypocalcemia treatment in children, and
17 kidney stones and those kinds of things.

18 DR. WARD: In which patient population? Are you
19 talking about children with myelomeningocele incumbency?

20 DR. GROGG: Just in general. If they are
21 passing RBCs in the urine and it turns out that it is a
22 calcium problem, most of these kids with one milligram per

1 kilo of HydroDIURIL.

2 DR. WARD: Rose.

3 DR. HIGGINS: I'm Rose Higgins. I'm a
4 neonatologist from the Pregnancy and Perinatology Branch.

5 Can you guys hear me?

6 PARTICIPANT: Yes.

7 DR. HIGGINS: We did have a newborn drug
8 development initiative which occurred last March, and
9 there were many experts from around the country that
10 participated in that. One of the working groups was
11 focused on bronchopulmonary dysplasia, and these issues of
12 the Thiazide diuretics came up markedly.

13 The problem with determining growth and
14 neurodevelopmental outcome in children with BPD is that it
15 is so confounded by all the other factors that are going
16 on in the nursery, and I think that is why this was moved
17 forward for the hypertension as opposed to the BPD
18 indication in order to get information for labeling.

19 PARTICIPANT: I can see exactly -- I'm a
20 neonatologist as well -- how that would have come about,
21 but I think the reality is, in the NICU in the acute care
22 setting, we very seldom would reach for a Thiazide as our

1 first-line treatment for hypertension, as opposed to the
2 treatment of BPD. At least in our unit in our area in the
3 west, many of these kids go home on long-term treatment
4 and we really have very little information about
5 electrolyte imbalance efficacy and also adverse effects.

6 DR. WARD: Yes.

7 DR. GROGG: Just a final comment from me is that
8 you also need to monitor the electrolytes initially, and
9 that may increase the cost.

10 DR. WARD: Yes, there is no doubt about it.

11 Okay. Other comments?

12 [No response.]

13 DR. WARD: I will try to get the order correct
14 this time.

15 Should we go to Acetylcysteine for Acetaminophen
16 poisoning.

17 Dr. Berquist.

18 **Review of Acetylcysteine**

19 **Dr. William E. Berquist**

20 DR. BERQUIST: Again, I want to thank you for
21 inviting me. My bias is from pediatric liver transplant
22 and pediatric TDI, so I guess I'm the only one. I'm also

1 biased towards the San Francisco Giants.

2 [Laughter.]

3 DR. BERQUIST: I wanted to use my time to have a
4 little bit -- [off mic].

5 DR. WARD: Could you move the mic down a little
6 bit closer?

7 DR. BERQUIST: Okay, thank you.

8 So, Acetylcysteine is actually a precursor to
9 Cysteine, which is necessary for -- [off mic.] The charge
10 was to look at Acetylcysteine and Tylenol overdose
11 poisoning.

12 So I think that the main reason for this is
13 because Acetaminophen toxicity and poisoning is probably
14 one of the most common overdoses that one runs into.
15 Acetylcysteine is actually a fairly old drug because it
16 has been around and studied, as a number of these, in the
17 '60s and '70s, and from that came the guidelines that have
18 been drawn up and have been fairly well established. So
19 much of the use of it has been previously established and
20 the application to children has been utilized.

21 There have been some controversies about the use
22 of it in particularly Chinese formulation versus the world

1 formulation. In the United States, primarily the world
2 formulation is used.

3 DR. WARD: Let's just pause a second. Do you
4 want to go ahead and bring that file up?

5 [PowerPoint presentation.]

6 DR. BERQUIST: So one of the major issues with
7 it are the side effects in its use. So one runs into a
8 fairly substantial proportion of the children having
9 problems with nausea, as well as adults. So this is the
10 structure.

11 Again, Acetaminophen is only about 5 percent.
12 So this is Acetaminophen, and it is converted to the
13 sulfate of the glutathione. About 5 percent is detoxified
14 through glutathione or conjugated, and this leaves a small
15 percent which is down at the bottom -- [off mic] which is
16 really the pre-form, which is damage.

17 This is another slide which shows that most of
18 it is really excreted, but you have glutathione depletion
19 which ends up resulting in hepatocellular necrosis.

20 So one gives the Acetylcysteine to provide the
21 cysteine for glutathione. This is where this -- [off mic]
22 is vitally used, again established predominantly in

1 adults, with the level of Acetaminophen in the blood
2 guiding whether or not there would be hepatic toxicity.

3 Now, I might remind you that, again, in adults,
4 most of this is from an attempted suicide. In children,
5 they may be getting toxic doses over a period of time.
6 These are the three forms of treatment. There is a 72-
7 hour PO, a 20-hour IV, and a 48-hour IV regimen.

8 The labeling is such for pediatric patients that
9 there is only one study, and that is actually in newborns,
10 looking at the IV infusion of Acetylcysteine, but there
11 are really no controlled studies in pediatric patients.

12 One does not find any randomized control studies
13 because this is a fairly well established treatment. The
14 only other option is what I do, liver transplant.

15 [Laughter.]

16 DR. WARD: It is a tough control group.

17 DR. BERQUIST: It is a tough control group.

18 I think the major issue here is the warnings of
19 the anaphylaxis and the actions especially in IV, as well
20 as the other adverse effects in the world, but these are
21 the issues that apply. I think probably that this is a
22 common problem that you have this toxicity, but really, it

1 is the only major treatment.

2 This was an open label study which was done by
3 Perry and Shannon looking at the toxicity. Again, this
4 reemphasizes that if you give the medication within 10
5 hours of ingestion that it is very effective, as compared
6 to those who aren't getting it.

7 This study is acute Acetaminophen poisoning in
8 children. Kids are not just little adults. This was a
9 single case report recently from Chicago where this child
10 had a very high level, a five-hour level, 863 micrograms a
11 milliliter, and the point was this child did very well
12 with hemodialysis and Acetylcysteine therapy. Their case
13 represented the largest reported ingestion under 18 months
14 who recovered.

15 This particular study was the one out of all the
16 slew of articles which really looked at sort of a meta-
17 analysis of what studies were available. It was from
18 Buckley [ph.] I think that they are from New Zealand.
19 They compiled over 900-some cases looking at outcome of IV
20 versus oral and basically showing that they were fully
21 effective in terms of the outcome.

22 These actually are the only studies that they do

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1 compare, looking at the treatment delay and outcome with
2 the IV versus the oral. They did a comparison of with and
3 without hepatotoxicity, again showing that late
4 presentation and high-risk concentration were major
5 factors, especially the delay in receiving Acetylcysteine.

6 So their conclusion in these 981 occasions is
7 that the differences probably are factual and relate to an
8 appropriate subgroup analysis. A shorter hospital stay,
9 patient and doctor community, and concerns over the
10 reduction of bioavailability make intravenous preferable,
11 but really, the differences are not really substantial.

12 So these are the adverse reactions. Again, they
13 are usually manageable, but they represent about 60
14 percent or so of cases. Again, this particular paper
15 looked at risk factors for adverse reactions to
16 Acetylcysteine, and their conclusion was the major risk
17 was in asthmatics. Again, most of these reactions can be
18 managed very successfully.

19 This particular paper points out that one of the
20 problems we run into in infants and children is that they
21 may be given multiple doses rather than a single large
22 dose of Acetaminophen. So they may accumulate a higher

1 dose and therefore trying to use it in those particular
2 cases may not be appropriate. They devised a
3 recommendation that you really look for hepatic injury.
4 Those are certainly going to be your highest-risk
5 patients.

6 So as I reviewed it, the number of cases that we
7 see actually in infants with Acetaminophen poisoning where
8 it really causes a problem is actually very few. In my
9 experience, we actually did a three-center study, and most
10 of our patients are easily managed with Acetylcysteine,
11 either oral or IV, and we haven't had to do transplants
12 except for in those particular cases where it was very
13 delayed and where there were other drugs. So that pretty
14 much mirrors what you see in the adult group.

15 So I think my ranking for studying this, at
16 least for Acetaminophen toxicity, because it is not that
17 common except for adolescents -- and there I think the
18 data is such that you can pretty much use adult data -- is
19 that I didn't see a big role for further studies. I think
20 I gave it a score of three.

21 What I did think is that in our area of dealing
22 with acute liver toxicity, increasingly Acetylcysteine as

1 a scavenger and to help scavenger free radicals to help
2 the liver recover is more prevalent. For example, in
3 neonatal iron storage disease, we are seeing a number of
4 infants who have an iron overload, and in that particular
5 case, that has been used. It may prevent liver
6 transplantation. That is kind of a focused area.

7 You have a drug that is not going to be used in
8 a very large number of individuals, at least not the way
9 it is currently, and I think that there is a role in the
10 future to study this, because in the area of acute liver
11 failure, we do need other treatment protocols to kind of
12 help get these kids through that and hopefully get the
13 liver to recover. So that was my only concern, is we
14 might shift the focus towards that.

15 So, thank you.

16 DR. WARD: Okay. Tom?

17 **Secondary Review of Acetylcysteine**

18 **Dr. Thomas P. Green**

19 DR. GREEN: Well, I really have pretty much the
20 same comments as Dr. Berquist. Maybe just a little
21 summary of my own thoughts about it is that I was struck
22 in looking at the literature provided about this

1 discrepancy between the recommendation for IV use outside
2 this country and the recommendation for oral use within
3 this country of Acetylcysteine for Acetaminophen
4 poisoning.

5 I guess those of us that are insecure about so
6 many things that the insecurity about giving an oral
7 medication in a nauseated, vomiting child who has a very
8 high risk for potentially fatal outcome of the underlying
9 poisoning, I'm pretty insecure about that. I think
10 translates in other people's insecurities to long lengths
11 of stay and just a feeling of not giving the best therapy
12 for the child.

13 So that, in my view, the ability to study this
14 drug and its allay of some of the concerns about the
15 toxicity or the incidence of side effects of the IV
16 preparation would be fairly useful and, in addition, in
17 developing bioavailability information. So one could
18 actually, perhaps, study better the oral medication and
19 thereby be more confident about its use, even though I
20 acknowledge that the literature does show pretty similar
21 outcomes.

22 So that's where I come down.

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1 DR. WARD: Dr. McCune.

2 **FDA Review of Acetylcysteine**

3 **Dr. Susan McCune**

4 DR. McCUNE: I can't add to Dr. Berquist's
5 wonderful summary about this drug except to add that there
6 are no adequate and well controlled studies documented in
7 the label, which is a problem in that the PK information
8 is only in 500-grammers. We try so hard to get studies in
9 500-grammers, and it is interesting that this was the one
10 that we have.

11 [Laughter.]

12 DR. McCUNE: Speaking of BPD and those issues.

13 I think two of the interesting conditions that
14 you talked about are, one, the chronic use and toxicity
15 associated with that that has not been very adequately
16 studied; and then, at clinicaltrials.gov right now, there
17 is an adult study ongoing for acute liver disease not
18 associated with Acetaminophen toxicity. So I think to
19 then expand that into the pediatric population would be
20 excellent.

21 **Open Discussion**

22 DR. LOPEZ: My name is Lolita Lopez, medical

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1 officer from GI. I only have one comment to make, and
2 that is to let you know that in the label it is stated
3 that the elimination half-life for Acetylcysteine is
4 longer in newborns, about 11 hours, compared to that in
5 adults, which is 5.5 hours.

6 The PK information is not available in other age
7 groups. So we have the adults and the tiny babies.

8 DR. WARD: Could I ask you both, and FDA as
9 well, to comment upon the toxicity? I was struck with the
10 New Zealand study that showed, out of 900 patients, I
11 believe, there were two or three with hypotension. As a
12 neonatologist, my impression of the literature was that
13 hypotension with intravenous therapy was more common than
14 that and was actually a significant issue.

15 PARTICIPANT: Well, again, I think these
16 particular patients are at risk for hypotension anyway
17 with liver failure, so you have kind of a rough set to
18 work with.

19 DR. WARD: Is there merit in a study that
20 evaluates intravenous versus oral therapy? It sounds like
21 you would say yes.

22 DR. GREEN: Yes, absolutely. Again, developing

1 the bioavailability information might lead to more
2 confidence in the oral form, therefore the shorter lengths
3 of stay, I guess, eliminating the IV use.

4 DR. SNODGRASS: We probably treat about 100 a
5 year, adults mostly, with this, and the IV has come out
6 recently. Of course, it is more expensive.

7 If you look at the oral use, 80, 90 percent or
8 more, what you absorb early is going to go through the
9 poor vein. So you get about 60, 70 percent oral at least
10 absorption, and that is really markedly decreased for
11 oral.

12 In the first 10,000 cases in the United States
13 in the Acetaminophen trial orally, there was not one case
14 of anaphylaxis. In the first 25 IV when it was given
15 rapid bolus in the U.K., very rapid, probably disrupting
16 sulhydra [ph] bonds and plasma proteins, they had a case
17 of anaphylaxis. So I think that is one issue about the
18 IV, is the slowness of the use.

19 The other is, if you have a six-fold difference,
20 if it is six liters per minute output in an adult and it
21 is one liter per minute going to the liver when you give
22 it in IV, then only a portion of the IV is hitting the

1 liver. So you see your end of the curve won't show you
2 what is getting into the liver from the oral. That is why
3 the oral works so well, even though they vomit. They
4 actually absorb it. It smells awful. It is rotten eggs.

5 So I think these are issues to be addressed, and
6 they are important issues. I think the extension of this
7 into the liver prevention areas or treatment areas beyond
8 Acetaminophen, pediatric nephrology has some literature
9 about interstitial nephritis. I know I have been called
10 by nephrologists about the dosing, as well as other
11 issues.

12 So I think there are other uses for this down
13 the road, and the IV will have a real place. It is
14 defining what those issues are.

15 PARTICIPANT: I think the portal circulation is
16 certainly a pertinent issue with respect to the
17 bioavailability.

18 DR. BLUMER: I guess we need to keep two things
19 in mind. First of all, with respect to the
20 pharmacokinetics, there hasn't been any link between
21 pharmacokinetics and pharmacodynamics with this drug. So
22 having that data I'm not sure is going to help us a whole

1 lot. I mean, it is probably easy to get, but it is not
2 going to be as useful in determining the effectiveness or
3 safety of the drug.

4 I think, to echo some of Bill's comments, the
5 likelihood of significant toxicity in young children is
6 really very, very small. I think that the literature that
7 I'm familiar with would show that with exposures under 300
8 milligrams per kilo in children under 16 to have
9 significant hepatotoxicity, you really have a very rare
10 problem.

11 So I think we have to just keep those things in
12 mind as we look toward this. Our experience in the ICU as
13 well is that the oral is actually very well tolerated.
14 The kids that do vomit respond fairly well to
15 Noandanzitron [ph] or a drug like that, and then tolerate
16 the medication. There are at least theoretical reasons
17 why the oral formulation might be better, but I think at
18 the end of the day, after the 20-hour regimen or the
19 couple of days it takes you to give the oral regimen, you
20 won't see anything in our patients.

21 So I just think we have to weigh all those
22 things. I mean, there is a great desire to get data. I

1 think the future for Acetylcysteine is in other areas, and
2 the other area, I think, is in terms of end organ
3 protection and things like that, where there may actually
4 be some good PK/PD models that could be developed. That
5 may be a more important indication.

6 DR. WARD: Yes, Stan.

7 DR. GROGG: Good old Muco Mist. Those of us old
8 enough to remember, they used it in the nebulizer, and the
9 smell, and it actually made the asthma worse rather than
10 better, but we didn't realize that.

11 Where I see its use is in the 18-month to three-
12 year-old that Tylenol is the number one ingested overdosed
13 or accidentally ingested medication in pediatric use. So
14 I would like to see some more studies. I was surprised it
15 hadn't been approved, because that is what we reach for
16 immediately if we see a child with an overdose of Tylenol.

17 I would like to see some studies on the safety and its
18 use.

19 It has to be used somewhat not knowing what type
20 of plasma values you may get if charcoal is already in the
21 stomach, too. You tend to give charcoal immediately for
22 any type of overdose.

1 DR. WARD: Wayne.

2 DR. SNODGRASS: The charcoal data was some years
3 ago. It doesn't bind it very much, so that is not much of
4 an issue for that particular aspect.

5 DR. WARD: That is charcoal binding and
6 Acetylcysteine?

7 DR. SNODGRASS: Right.

8 PARTICIPANT: That does not affect it, so it
9 still works.

10 DR. WARD: Steve.

11 DR. LAWLESS: I have a question for Dr. Blumer.
12 I was struck by your comment about the pharmacokinetics
13 and essentially the discordance there with this drug in
14 particular. If you are calling for studies for that and
15 that is a discordance, and given the idea that you have no
16 other option, you don't give the option as liver
17 transplant.

18 DR. WARD: Right.

19 DR. LAWLESS: Doing studies on it, if you are
20 starting to compare it to other drugs in terms of
21 prioritization, I'm trying to find out a real reason to
22 highly prioritize the drug to study. What is the end

1 goal? I mean, would you put somebody in a study where the
2 end point may be liver transplantation?

3 DR. BLUMER: I think the ethics of that are
4 lacking, so.

5 [Laughter.]

6 DR. LAWLESS: We are in America.

7 DR. BLUMER: I think the real issue is whether
8 Acetylcysteine at this point in time can be used safely
9 and effective for Acetaminophen overdose or for oxidative
10 protection with what we understand about it now, or
11 whether our use and children's health will be improved by
12 further study. That, I think, is really the issue. This
13 is not on the list for placebo control trials.

14 DR. WARD: Any other comments or discussion?

15 [No response.]

16 DR. WARD: If not, let me just remind you, check
17 your forms.

18 We will take a break. As Dr. Alexander pointed
19 out, we are ahead of time. Why don't we resume about
20 10:45. I'll look to the boss. Okay.

21 [Laughter.]

22 DR. WARD: All right, 10:45.

1 [Break.]

2 **Review of Clonidine**

3 **Dr. Julie Magno Zito**

4 [PowerPoint presentation.]

5 DR. ZITO: I'm really delighted to be here. I
6 wish I were better prepared. The events of the last two
7 weeks have been incredible, with the FDA's announcement of
8 the Black Box and child psychiatry is just in a frenzy out
9 there about what are we going to do, what sort of
10 monitoring, and so on. So I have been listening to a lot
11 of that at your annual meeting for numerous things last
12 week.

13 I have two approaches to what I would like to do
14 here. First, I would like to show you some empirical data
15 that, thanks to Dr. Lasky and Dr. Mattison, we at the
16 University of Maryland -- and I want to acknowledge my
17 colleagues, two of them who have helped work on data
18 analysis are here in the audience: Dr. Dan Safer, who is
19 in child psychiatry and more or less knows whatever I
20 know, and then Mecale Menis is the research assistant.

21 I'm just going to say two things to remind
22 ourselves of what our task is. One is to focus on the

1 value of funding and conducting additional studies, and
2 then, secondly, to think of what scientific questions and
3 what types of study designs we would like to do to advance
4 the science.

5 So let's move now to the question of what is the
6 story on Clonidine. The information you gave me mentioned
7 autism and ADHD, and I think somewhere else that I saw
8 hypertension, as diagnoses that you were interested in.

9 The Metaworks people did a huge printout. It is
10 enormous and is quite a potpourri of uses of Clonidine
11 across all varieties, including surgical, sedation,
12 insomnia, and so on. I'm really going to stay much more
13 narrowly focused on the mental health-related issues.

14 I have a Mid Atlantic Medicaid State Database on
15 which I'm going to show you some utilization. Everybody
16 knows Clonidine and Guanfacine are examples of drugs that
17 are in the category of alpha-agonists. They pretty much
18 have had very, very little pediatric use until recent
19 years.

20 The first reports of Clonidine use for mental
21 health problems came, I think, with Michael Hunt's paper
22 around 1988. Beginning in the early '90s, all the curves

1 that we have shown in looking at trend usage, there is
2 this huge increase in use of all psychotropics virtually,
3 with the exception of narcoleptics, lithium, and some of
4 the drugs that are nastier and reserved for more severe
5 situations. But this group of drugs went from nothing
6 into something on the charts.

7 The other point is really just these two
8 examples that I know about that get any usage in mental
9 health, and the second thing to say is that most of it
10 represents the use of Clonidine and then, to a smaller
11 extent, Guanfacine. That is sort of the way that they
12 appear in the literature, and that is the use.

13 If we were to look at the children zero to 17 --
14 so look at the last set of bars on the table -- you can
15 see that the use of an alpha-agonist runs with stimulant
16 use. That is to say that some proportion of children that
17 receive the stimulant are also now receiving an alpha-
18 agonist to deal with some of the problems with sleep, the
19 insomnia problems that occur in the evening. There is
20 possibly, also, a small number of them that get Clonidine
21 alone, but I think that group is much smaller.

22 Then if we split it out by age group, I would

1 make the argument that we are not looking at the
2 occurrence of hypertension. There is no diagnostic
3 information on the slide, so I'm making it all up as we go
4 along here. But if you look by age group, you can make
5 the case that since stimulant use really takes off
6 beginning with the school-age kids, that pattern is pretty
7 consistent with use for ADHD.

8 That is, again, just showing you that most of it
9 is Clonidine.

10 Now, the nice thing about the Medicaid data set
11 is that we have a variable that nobody else in
12 commercially insured populations and HMOs has, which is
13 very submissive, although that may be changing. I don't
14 know, maybe HMOs are starting to do that.

15 There are very pronounced differences in the use
16 of psychotropic medications according to race/ethnicity.
17 I think many of you who have been in treatment service
18 delivery for many years would understand that we have a
19 problem in terms of getting and keeping people in
20 treatment for chronic conditions over time if they are
21 poor, under-educated, come from different cultural
22 backgrounds, or have problems accessing services.

1 So all of those things probably contribute
2 particularly in the area of mental health, where there are
3 bigger disparities and bigger disagreements around how we
4 handle children with problems in hyperactivity, school
5 performance, getting along with their peers, aggression,
6 et cetera. So there is good reason, then, to understand
7 that most of the usage is white, and we should pay
8 attention to that.

9 In the gender use we also have a bias, because
10 we all know that boys are badder than girls. So there
11 they are in much larger numbers.

12 That's it for that part of the show. The rest
13 of the story is that I just ran out of time to get all
14 that stuff on the task sheets into PowerPoint. I
15 discovered at 10:30 last night that, oh, I guess the
16 worksheet isn't going to work from a Word file, so it
17 shows you how tired I was.

18 I will start my decision, and then we can work
19 backwards to some of the rationale.

20 So I'm on Task 1, the scoring sheet for
21 Clonidine, or Catapres, which is the brand. The
22 indications are autism and ADHD, but there is actually a

1 whole range of neuropsych conditions. Anything that we
2 can't fix with everything else we have in psychiatry,
3 there is a tendency to use what else is out there. That
4 is a messy statement, but it is a reality. I have been
5 reading the literature for 25 years.

6 Clonidine came from adult use in schizophrenia.
7 That is its root into child, which is really a pity
8 because it didn't work and it was shown to be a
9 considerably more dangerous drug.

10 You know what? I don't know how to do this.
11 I'm very challenged here. Maybe you can move the screen
12 for me.

13 My overall score is nine, so very high on
14 getting this drug on the list. The reason for
15 pharmacokinetics and pharmacodynamics, I had nothing to
16 say. Basically, I really don't know. I didn't see in the
17 literature I reviewed any sort of detail or attention to
18 this, but the drug has been around a long time. Mecale,
19 it was marketed what, since? I forget. We ran down the
20 years. '80-something. No?

21 DR. WARD: Catapres as an anti-hypertensive was
22 available in the '70s.

1 DR. ZITO: Yes, the '70s, so it is even longer.

2 So when you have that long an experience with a drug, it
3 is undoubted that kinetics have been done at least in
4 adults. Now, what that means for us I have no idea.

5 The next category I can't see.

6 DR. WARD: Why don't you just go ahead and read
7 from that list of criteria? I think we have all worked
8 through them for our individual drugs, so I think we will
9 be familiar with them.

10 DR. ZITO: I'm sorry.

11 DR. WARD: That's fine.

12 DR. ZITO: I was going to sit over there and
13 just do it. I'm sorry.

14 So in terms of efficacy information, there is
15 available data, and now I will go back to telling you
16 about studies of this drug. There are 10 studies that I
17 reviewed for these mental health purposes. So we did
18 about 10 studies on a whole range of mental health
19 conditions.

20 Now I'm back to where the neonatologists and
21 others were talking earlier, which are small-end, open
22 studies, short-term use, and very unconvincing results

1 that would be easily driven by the enthusiasm of
2 investigators. So I'm not persuaded that the data are
3 very strong for things like autism. There are two studies
4 that are both open. Even the investigator's abstract
5 reads with a feeling of equivocal findings.

6 In regard to the studies that deal with things
7 like Turrets, again they have a large advocacy group, a
8 research study group, so the end is larger, but a lot of
9 limitations in terms of design.

10 A large set of concerns about safety of
11 Clonidine in young children because of the developmental
12 potential for changes in the cardiovascular system. There
13 is also a very large concern around accidental poisoning
14 and toxicities, which have been shown to be pretty
15 serious, and growing because the numbers of utilizers in
16 the pediatric population is growing.

17 So the younger sib of the child who has started
18 on it is now able to go on the kitchen table and poison
19 himself accidentally. So those are all big concerns and
20 sort of rationale for why we would want to know more.

21 Of course, it is not a hospitalization issue
22 except in cases like autism or very severely impaired

1 pervasive developmental disorders, stuff like that. On
2 the other hand, it is a very large proportion. From my
3 figure, it would be legitimate to guess that there could
4 be as many as 700,000 children in a given year who get
5 exposure to Clonidine.

6 Of course, for some of them it is going to
7 become a chronic condition because ADHD or whatever may
8 then move on and could be a harbinger of other severe
9 mental health problems to come.

10 The other thing we have learned in studying
11 these is that it is not even likely that we could stop
12 with just a stimulant and Clonidine combination and say,
13 wow, there have been serious questions about that. There
14 was debate in the literature. FDA people were involved in
15 wondering whether that was really a deadly combination.

16 The sort of general impression is, it is not a
17 deadly combination unless you really mess up and come up
18 with a very complex regimen in which all bets are off. So
19 high-dose use of Clonidine with a high dose of
20 Methylphenidate would predispose to that. Throwing in
21 other drugs that are known to really have serious
22 cardiovascular effects, like the TCAs, would be a good way

1 to find mortality.

2 So that's the story on the scoring. My general
3 comments around it are that it seems like the trajectory
4 around mental health is going in one particular direction,
5 and particularly because so much of this usage occurs in
6 primary care, we need to give pediatricians and family
7 practice doctors as much help as we can in assuring them
8 that we have a good literature about what they are using
9 and then eventually good clinical monitoring that would go
10 along with it.

11 I don't know what else I need to say about it at
12 this point.

13 DR. WARD: Dr. Grogg?

14 **Secondary Review of Clonidine**

15 **Dr. Stanley E. Grogg**

16 DR. GROGG: I will start off. I'm a general
17 pediatrician, and we feel like psychiatrists because we
18 are now forced, because of the inadequate supply of
19 psychiatrists, to learn about these drugs. We see a lot
20 of kids with ADHD.

21 [Pause.]

22 DR. GROGG: Anyway, so we have a large

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1 ambulatory clinic in Tulsa, Oklahoma, for which we see a
2 lot of ADHD kids. Because of the lack of pediatric
3 psychiatrists, we get to take care of these kids.

4 Just what is ADHD, so you know. I'm going to be
5 a boxing promoter when I grow up. It is impulsivity,
6 inattentiveness, and hyperactivity. Now, I don't think
7 anybody in this room has these conditions but our
8 associates do, so we have to work with them quite a bit.

9 First-line medications at present, just trying
10 to figure out which medications to go with with the kids,
11 are stimulants, the Ritalin compounds, and the amphetamine
12 and extra-amphetamine compounds. We are the capital of
13 the world in methamphetamine in Oklahoma, so we are kind
14 of careful with amphetamine compounds there.

15 A lot of non-stimulants are now available.
16 Seventy to 80 percent of the kids will respond to
17 psychostimulant medication, but there are a lot of newer
18 medications, such as Strattera, that are available as a
19 non-stimulant, and Wellbutrin, Effexor, some of the other
20 SSRIs. Catapres and Tenex are the drugs that are
21 available for us to look at and try to decide which is
22 what indication or those kind of things. It is very

1 difficult.

2 As was mentioned, Catapres, or Clonidine, is a
3 centrally-acting alpha-agonist used for hypertension in
4 the past. It has been shown to have central effects so
5 that it has been utilized for ADHD and some other
6 psychiatric disorders, as alluded to by Dr. Zito.

7 Plasma levels peak about three to five hours.
8 Thus, it is at least a PID with a half-life of 12 to 16
9 hours of PID dosage, which makes it difficult if you are
10 just using it specifically for ADHD.

11 Safety and effectiveness below the age of 12 has
12 not been established. Most of the studies have been above
13 five years of age, and younger than that there are very
14 few studies available.

15 It needs to be so heavily hydrated because of
16 the drowsiness and sedation, and this is where I have a
17 difficult time recommending it. If you look at what I put
18 there, it is very confusing, and it is very confusing to
19 the PCP out there as to how they would utilize Clonidine.

20 Not many PCP physicians who are overloaded with ADHD kids
21 would probably utilize it because of its confusion. Three
22 to five micrograms per kilo per day PO div tid-qid dose.

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1 I just throw this in here not for you to know how it is
2 utilized but how complicated it is.

3 On the other end of the spectrum, if the child
4 runs out, sometimes insurance only gives you a month's
5 supply and then forgets about it because they are ADHD or
6 the parents are ADHD, too. At the end of therapy, there
7 may not be enough medicines to go through the weekend and
8 they can have a secondary withdrawal type of symptom of
9 hypertension, a rebound effect of hypertension, so there
10 are some safety issues here.

11 Hypersensitivity to the drug class. You have to
12 use caution, since it is an adrenergic stimulant, in
13 coronary artery disease, cardiovascular disease in the
14 kids, or if they have liver function or renal function
15 limitations. There are a lot of drug interactions. I
16 won't list them all. I will just show you there are a lot
17 of drug interactions with this particular medication.

18 Adverse effects. The number one thing, and it
19 is what we use it for; a lot of us will use
20 psychostimulants such as Ritalin and then give them
21 Catapres at nighttime in order to help their sleep if they
22 have a history of insomnia, and that is probably the

1 number one of use of it with ADHD.

2 So, the cost. It is not too expensive.

3 So, in conclusion, often used in combination for
4 sedation for sleep with psychostimulants rather than a
5 drug by itself. It is difficult in my trade if you are
6 using it just for ADHD. There are many potential side
7 effects. There were three to four deaths reported back in
8 1999, and in the autopsies, it did not look like the drug
9 had actually caused those deaths, but there are some
10 questions about that.

11 You must withdraw gradually, which is very
12 difficult in ADHD kids, because if they run out, they just
13 stop taking it.

14 So, 20 to 30 percent of the kids with ADHD do
15 not respond to psychostimulants, and we need an
16 alternative drug. I would rather see Tenex, or Guanfacine
17 may be a better choice to look at rather than Catapres or
18 Clonidine. It is the same class, but it gives you a
19 longer duration of action and sedation. My recommendation
20 is to look at something different.

21 Although I gave it a score of 10, that is
22 because there are a lot of studies out there. Even though

1 I gave it a score of 10, my recommendation is that this
2 drug and its indications be a low priority for future
3 listings and discussions.

4 It seems to help more for autism. There were
5 only two studies that I could find. It seems to help more
6 if you have mental retardation associated with autism,
7 which is usually not the case. There are too few studies.

8 The two that were present did not show a significant
9 efficacy, to my mind, to recommend that we look at it
10 further, so I recommend that this drug and indication
11 receive low priority for future listings and discussions.

12 With that, it is time out, folks. Effects of
13 gas.

14 DR. WARD: All right. With that closing --
15 [Laughter.]

16 DR. WARD: Let's see. FDA, Dr. McCune again.
17 You are on.

18 **FDA Review of Clonidine**

19 **Dr. Susan McCune**

20 DR. McCUNE: I think Dr. Sheridan is going to
21 join me.

22 It is tough to follow that.

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1 I think a lot of the issues have been brought
2 forward, and there could certainly be a lot of discussion
3 about this drug. The use is extensive from a
4 neuropharmacologic perspective, but the label reflects
5 none of that. The label only reflects the anti-
6 hypertensive use of the drug.

7 I think it is also important to note that from a
8 basic science perspective, alpha-2 adrenergic receptor
9 subtypes change dramatically in the brain during
10 development in rats, so I think that there is certainly a
11 need to look at this over the course of development in
12 terms of responses to this drug.

13 I would like to reemphasize the fact that there
14 are significant safety effects that are worrisome,
15 especially the cardiac side effects. The accidental
16 overdose issue is not trivial now that this drug is being
17 used extensively off-label. There are a lot of
18 opportunities for siblings to get a hold of this. There
19 are also reports of the patch version of this actually
20 being associated with overdoses.

21 So I think that there is a substantial amount of
22 use going on. There is no information in the label, and I

1 think that there are significant safety concerns that
2 would worry us.

3 **FDA Review of Clonidine**

4 **Dr. Alan M. Shapiro**

5 DR. SHAPIRO: I certainly agree with all that.
6 I think the two speakers have put out Clonidine very
7 effectively for our consideration.

8 I would urge consideration for a high priority
9 for this drug simply because it is being used extensively.

10 I am pediatric neurologist whose background is mostly in
11 epilepsy, but I know among my fellow pediatric
12 neurologists and probably among general pediatricians,
13 this is a medication that tends to be used not only for
14 trying to calm down patients that require stimulants and
15 can't sleep well, but also, in other developmentally
16 disabled children that need some form of sedation at night
17 in order to be able to settle down and sleep, Clonidine is
18 often used.

19 As Dr. McCune has just pointed out, the more it
20 is used, the more the potential risks, particularly when
21 we go past specific pediatric safety data and we don't
22 have a specific preparation for pediatric which might be

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1 also be considered. We rely on the parent to chop the
2 tablet in half and dissolve it, or whatever, putting it in
3 applesauce, and so forth. There are more and more
4 problems if you have multiple caretakers for a child,
5 problems with accidental overdosing, and of course, the
6 younger sibling problem.

7 **Open Discussion**

8 DR. WARD: So there is no liquid formulation at
9 this point?

10 DR. SHAPIRO: Correct. We only have the 0.1
11 milligram tablets and the 0.2 and 0.3, that's it.

12 DR. MEYTHALER: I'm a PMNR doc, and there are
13 drugs being used a lot more off-label based on adult
14 studies than people realize. It is being used a lot in
15 spasticity and chronic pain. It is actually being used in
16 Europe for both pain and spasticity, and it is being
17 compounded in the United States frequently for this. Some
18 of it is filtering down now into the pediatric population
19 big time.

20 The other thing is that there are alternatives,
21 and nobody has brought up the issue. This is an alpha-2-
22 agonist. There is a lot of off-label use for all the

1 indications you guys have been talking about with the
2 Tizanidine. It is an interesting issue because Tizanidine
3 is one-fortieth the alpha-1 effects of Clonidine on blood
4 pressure, but most all of it is alpha-2 effect.

5 So both of these drugs are being used relatively
6 heavily in the populations, but there is an alternative
7 out there for alpha-2s. It is kind of interesting nobody
8 brought that up. I thought I should just kind of bring
9 that up.

10 There is a third thing. Clonidine is being used
11 a lot for sedation in agitated head injury patients, and
12 I'm a head injury doc. The problem is that there is
13 animal data out there indicating slow neural recover in
14 neurological conditions acutely.

15 DR. WARD: First, we can't bring up a new drug,
16 I think, at this point.

17 DR. MEYTHALER: I know, I know, but you do have
18 listed other alternatives as well.

19 DR. WARD: Exactly, right.

20 DR. MEYTHALER: One was Guanfacine. I saw on
21 the list that some people are using Tizanidine too, I
22 think.

1 DR. WARD: I think we are hearing a nomination
2 for next year's list.

3 Are you suggesting that traumatic brain injury
4 should be part of the issues studied with Clonidine?

5 DR. MEYTHALER: Not at this point in time, but I
6 do think that you do need to add in the spasticity and
7 pain because that has heavy uses and there wasn't anything
8 brought up about that.

9 DR. GROGG: Just to mention, it is available in
10 a patch that can be put on the child so that you can
11 utilize it that way, but it is about a 25 percent
12 incidence of skin reaction to the patch. They can't
13 tolerate it.

14 I would agree; I think it needs to be
15 investigated, just not for ADHD specifically. I think
16 that there are other drugs available and it has been shown
17 to be safe and effective for ADHD. For other conditions,
18 that is a different story.

19 DR. BLUMER: I actually just have a question
20 about what I just heard from the FDA. One of the
21 motivations that I'm hearing for considering this is
22 because it is used. I wonder whether that is a good

1 enough indication for developing a study. I would
2 question whether, if it is being used and the use is
3 inappropriate or wouldn't be recommended, should we
4 promote it?

5 I look at the sedation with Clonidine as an
6 adverse effect, and now we are almost advocating that
7 because it is used constantly for an adverse reaction we
8 should then study it. I wonder if we shouldn't say, "Stop
9 doing that." I mean, it is a drug that in some respects
10 has a narrow therapeutic index, certainly narrower than
11 many of the other drugs we have considered so far this
12 morning.

13 I just worry about using use data to drive a
14 process like this if the use isn't rational.

15 DR. LASKY: I think this hits at one of the
16 cruxes of what BPCA is meant to address, and I was going
17 to ask Stan about this. It scores highly, and you seem to
18 be recommending against studying it because you are not
19 pleased with the way it is used, but maybe the question to
20 ask is, do we need to do a study in order to tell people
21 to stop using it.

22 If your instincts are telling you that it is an

1 improper use, then is studying it a legitimate thing to do
2 in light of how many people are using it and believing
3 that it is an option.

4 So I'm trying to say that we need to separate a
5 little bit our judgment on the use from a judgment on
6 whether we should study it. They are not the same thing.

7 DR. WARD: Dr. Sachs, and then Dr. Zito.

8 DR. SACHS: There is a place in the label that
9 if there is sufficient off-label use and it is actually
10 inappropriate, and there is evidence that that is the
11 case, that you can change the label to state that.

12 DR. WARD: Dr. Zito?

13 DR. ZITO: I would like to respond to Dr.
14 Blumer's question, because I agree with you that all of us
15 with any training in clinical pharmacology come from a
16 very structured approach to the use of drugs. In the last
17 15 years, there have just been innumerable examples that I
18 can point to for the utilization of drugs whose adverse
19 effect is really essentially the desired effect.

20 Now, having said that and being practical, we
21 have over a half a million kids who are likely to get the
22 treatment, and whether they follow the Blumer effect or

1 the Zito effect is questionable.

2 [Laughter.]

3 DR. ZITO: Because we can preach all we want.
4 There are lots of folks now who are very comfortable.

5 So what I would urge us to do is to think about
6 whether we really want to do efficacy studies in a sort of
7 traditional way, whether we would want to focus on safety
8 and say we are really going to follow a very large cohort
9 of children and we are going to follow them over five
10 years so that we could see the changes in development, the
11 impact on development from age two to seven, something
12 like that.

13 DR. BLUMER: Or, is the question really to look
14 at the sedative effects in children with ADHD. I mean,
15 the implication I got was that you are going to look at it
16 as a drug for efficacy in ADHD, and that is my impression
17 of the use, too. It is used almost as an adjunct to
18 children receiving stimulants, to help them sleep at
19 night, et cetera; should that be the focus of the written
20 request.

21 DR. WARD: There was a Pediatric Advisory
22 Subcommittee, probably three years ago, specifically about

1 children being treated with stimulants and is it
2 appropriate to ask a company to study a soporific for aid
3 in sleep. The conclusion was no, yet the reality is, if
4 you are the parents and the child is off the wall, and it
5 is about midnight, you're going to reach for something and
6 you're going to call your doctor the next day and ask them
7 for something.

8 DR. LAWLESS: The question, actually, just along
9 the same lines, is, one of the problems that is going to
10 come up as you start talking about this drug, or any other
11 drug, is the specific setting, the IV form of this versus
12 this, but you are using a rationality of disease
13 management.

14 If the studies you are going to recommend
15 essentially going to be disease management studies, how
16 does it fit within ADHD treatment, or is it going to be
17 the specific drug itself and a very limited focus on the
18 drug.

19 DR. LASKY: I wanted to bring up the comments by
20 the National Institute of Mental Health. They
21 specifically recommended that the drug Clonidine be
22 studied for the indication of ADHD. They suggested that

1 PK studies are needed to determine the most appropriate
2 frequency of dosing. PK studies of both oral and TTS
3 preparations are needed. PK, when the drug is given
4 together with Methylphenidate, is also needed because
5 Clonidine is often used in combination with stimulant
6 medication.

7 They also said, in terms of the scientific
8 questions, placebo-controlled efficacy and tolerability
9 studies are needed to determine the therapeutic benefit of
10 this drug in isolation and when added to stimulant
11 medication.

12 General safety and especially cardiovascular-
13 adverse events and sedation and possible impact on
14 cognitive function. Also, presence and extent of
15 withdrawal symptoms needed to be determined.

16 I think Dr. Vitiello was going to be here, but I
17 don't see him.

18 DR. WARD: Stan.

19 DR. GROGG: Once again, as an ADHD drug, and I
20 think everybody is hearing this appropriately, I
21 personally do not think that it needs further evaluation.

22 As an adjunctive therapy for its side effect of sedation,

1 I think it does need to have further study. It does need
2 to be evaluated, but I was under the impression that the
3 recommendation is based upon just ADHD.

4 I think there are other medications available of
5 a similar type, such as Tenex, that have less side effects
6 if you are treating just ADHD.

7 DR. ZITO: To clarify what you are saying, I
8 think you are saying for the treatment of ADHD alone. In
9 other words, as monotherapy, which I would agree with.

10 DR. SACHS: I was just curious. I know the
11 place that I see this used mostly in my practice is in
12 kids with tics. I know that really hasn't come up at all
13 yet in the discussion, but I was actually curious about
14 the experience from the experts.

15 DR. GROGG: I would respond to that just from
16 the aspect that we have utilized Clonidine for kids with
17 tics because we think psychostimulants seem to make them
18 worse, but it seems that some of the newer drugs such as
19 Strattera and Tenex would work better with less side
20 effects.

21 DR. WARD: Do you feel like we have answered
22 your questions about people's focus as far as how they

1 feel this should be studied?

2 DR. SHAPIRO: Yes. I think it is very helpful,
3 certainly, from the point of view of the division. We
4 want to consider all these aspects when we come up to a
5 particular drug when it is recommended that may be
6 mentioned in terms of one indication, but we would
7 consider the other indications as well in crafting a
8 request for study through NIH contracts. So all of this
9 feedback that you are giving us is extremely helpful.

10 DR. MATHIS: I just quickly wanted to address
11 the issue of studying drugs because of amount of use. We
12 have actually looked at this several times and have
13 decided that from an ethical aspect it is not right to
14 simply study drugs in children because a lot of people are
15 using it.

16 It becomes a problem for us, though, when it is
17 in the common medical literature that a drug is used as an
18 adjunct treatment and it is being used off-label and many
19 people are writing about its effectiveness, especially
20 when there is a huge safety concern like there is with
21 Clonidine.

22 So sometimes we need studies to actually

1 determine whether or not it is effective. Of course, if
2 we had negative studies or a stronger safety signal that
3 we were able to identify, we would use that to educate
4 providers and we would also be able to get that into
5 labeling to prevent them from using it.

6 So some of the times, while we don't say it is
7 the use that necessarily drives our desire to have these
8 drugs studied, it is more a need for additional
9 information on the efficacy and safety of the drug because
10 of its being used so frequently that drives us to do the
11 studies.

12 DR. WARD: I think those are important points to
13 make.

14 Any further discussion?

15 DR. SNODGRASS: I just think that points out a
16 real ethical dilemma. At what stage do you reach the
17 ethical dilemma that we shouldn't do this. On the other
18 hand, you would like to have data. If you predict pretty
19 strongly ahead of time that this is going to be negative,
20 would you want your child in that study.

21 DR. WARD: Given the use information, if it is
22 likely to be a negative study, it sounds like there are a

1 lot of kids responding to placebo.

2 DR. SNODGRASS: A dangerous placebo.

3 DR. WARD: Given the hour, let's try to fit in
4 one more drug before lunch. There is a second blue sheet
5 beginning with Cefuroxime for infections in children with
6 sickle cell anemia. Dr. Snodgrass, I believe, is
7 presenting.

8 **Review 4: Off-Patent Drugs**

9 **Review of Cefuroxime**

10 **Dr. Wayne R. Snodgrass**

11 DR. SNODGRASS: This is an issue of Cefuroxime
12 and specifically its use in sickle cell disease. I think
13 this parallels to some extent Tom Green's earlier
14 characterization of, you have a drug that has a fairly
15 wide margin of safety where in fact there are essentially
16 no data in this particular selected indication, and yet it
17 is undoubtedly being fairly widely used in this group of
18 patients.

19 So it is not the same degree as Ethambutol,
20 where you have serious disorders, but you have perhaps a
21 number of other options from Cefuroxime, whereas with
22 Ethambutol in that setting, you may have fewer options.

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1 On the other hand, this is a potentially serious
2 disease. It is an infection that can be very serious,
3 particularly beyond the first many months of life, and
4 they can present and rapidly progress.

5 So I think it is fairly widely used. Its safety
6 is probably not much of an issue here. Again, Cefuroxime
7 is widely used in other soft tissue and other related
8 endpoints so that I think it is well recognized.

9 So the real question in prioritizing this is,
10 certainly from the point of view of this particular
11 disease, a study would be valuable, perhaps because there
12 might be some theoretical issues about renal function and
13 nephropathy down the line and this would be altered,
14 perhaps, or whether there would be less response in those
15 who are somewhat less immunocompetent with the asplini-
16 sm in particular. So there might be some reason to have
17 some advocacy in this and then perhaps some PK data,
18 particularly from the point of view of if it were handled
19 differently somehow.

20 I can't give it an extremely high priority, but
21 at least it would be, for those reasons, useful to do
22 that.

1 The other general comment I will have is that in
2 the labeling with regard to pharmacokinetics, it is stated
3 in the PDR at least that under age three months there is
4 no data, basically. Yet if you go to the USPDI, you will
5 see that in brackets it is down to one month or less, and
6 then between one month and three months of age, we have
7 specific dosing changes and say three to five times slower
8 half-life. So there must be data there which I haven't
9 found that somebody has reviewed.

10 So that is official compendia on the one hand,
11 but it is not in the PDR on the other hand.

12 So I gave it a score of seven based purely on
13 consideration of sickle cell disease per se.

14 DR. WARD: Do you want to make some secondary
15 comments?

16 **Secondary Review of Cefuroxime**

17 **Dr. Gary D. Overturf**

18 DR. OVERTURF: I think this is one of those
19 drugs that was indicated for sickle cell anemia primarily
20 based upon the fact that it was one of the earliest
21 cephalosporins with activity against Haemophilus influenza
22 and at a time that we did not have Haemophilus influenza

1 vaccines that were effective in young children.

2 The drug subsequently got a very checkered
3 career against Haemophilus influenza because of some PK
4 and PD data which really suggested that it did not achieve
5 good CSF levels. Actually, in one very famous trial which
6 appeared in the New England Journal of Medicine, it was
7 paired with another third generation cephalosporin.

8 So I think this specific indication is very
9 infrequently used because the rationalization for using it
10 primarily was based upon known pharmacokinetics, known
11 activity against the targeted infections in populations
12 that you wanted to use it in, and then known
13 susceptibility organisms.

14 Now I think there are better agents, and of
15 course, now there is also the problem of increased
16 resistance not only in Haemophilus influenza but also
17 streptococcus pneumonia.

18 So I think this has become kind of a moot point.

19 I think it is one of those historical indications listed
20 that has no rationale for use anymore. So this is a
21 question to me not whether you study it but whether it
22 should be delisted based upon what we know in terms of the

1 activity of this agent against current strains of
2 infective organisms. I'm trying to think of another
3 situation.

4 When we talked about anti-tuberculous drugs, it
5 was similar. You get to a point where there is such a
6 great resistance or such great problems that the drug is
7 no longer useful for what it was used for as a historical
8 indication. That is my perspective on this.

9 I don't know how you do that, but it is just not
10 a useful indication anymore.

11 DR. WARD: Let me apologize to Dr. Wiederman for
12 my confusion.

13 DR. WIEDERMAN: No problem. I will give you the
14 short version. I can't figure out why it is on the list,
15 either.

16 Although I will say in the package insert that
17 was on the CD, it was for the oral form of Cefuroxime, so
18 I don't know if there is a specific question about that.
19 Then I saw Dr. Lasky's slide at the start. There was a
20 particular question about its use under three months of
21 age in sickle cell disease. That is probably the age
22 range where sickle cell disease is not much different from

1 any other under three months of age. So if that is the
2 question, I don't see much reason to put it as a high
3 priority, either.

4 DR. WARD: The recommendation for it looks like
5 it came from NHLBI, and it specifically addressed under
6 three months of age with sickle cell disease.

7 DR. WIEDERMAN: They probably need some more ID
8 guys.

9 DR. WARD: Some more guidance, okay.

10 DR. LASKY: Well, that might be just exactly a
11 great solution to a problem, because people in different
12 fields don't necessarily talk to each other.

13 [Laughter.]

14 DR. LASKY: People put their names forward. It
15 would be interesting to continue this discussion back and
16 forth, because I don't like to disregard it.

17 DR. WIEDERMAN: I was originally thinking maybe
18 there were some things in the older sticklers with the
19 acute syndrome or respiratory things, but again, it is a
20 question of you can likely extrapolate, given that there
21 is such a wide margin of safety here, from other studies.
22 It would be interesting information but I'm not sure a

1 high priority.

2 DR. WARD: Dr. Shapiro and Dr. Alexander, do you
3 want to comment from the FDA?

4 **FDA Review of Cefuroxime**

5 **Dr. John Alexander**

6 DR. J. ALEXANDER: I found this a little bit
7 confusing, too, to understand what exactly was the
8 indication that was being sought. We don't actually have
9 an indication for drugs for treatment of sickle cell
10 patients or even for prevention of infection in sickle
11 cell patients. So I sort of found this confusing as to
12 what the goal was.

13 I agree with Dr. Wiederman's comment that the
14 current label for Cefuroxime basically covers children
15 down to the age of three months, and we are talking about
16 the oral formulation Cefuroxime. The reason that it sort
17 of stopped at three months was just because of the fact
18 that at the time that this drug was approved and labeled,
19 we were in an era where we weren't using oral drugs much
20 in children under two to three months of age.

21 So that is why that sort of cut-off was there,
22 is that they probably didn't have any data that they were

1 looking at in terms of the oral drug or its safety in
2 children less than three months and weren't expecting to
3 use it.

4 There is no population under three months
5 specifically with sickle cell disease where I think that
6 there is sort of a use for this. The question that I had
7 was, if the purpose is just we think that this drug is
8 valuable in treating infections that occur in sickle cell
9 patients, well, we think that the label sort of covers
10 this already because we don't necessarily treat those
11 patients with different doses unless they have some level
12 of renal impairment or something like that. So the drug
13 the way that it is labeled sort of covers that.

14 If the goal -- and this may be the case -- of
15 the NHLBI was to actually have Cefuroxime looked at as an
16 alternative to Penicillin for prophylaxis of patients with
17 sickle cell disease for sort of prevention of infection,
18 that is one potential where this could be a valuable drug
19 for study, but that would be looking sort of at the
20 efficacy, and there are a lot of questions about just how
21 valuable that would be in an age where they have Hib
22 vaccine, they have PCB-7 vaccine, and we don't necessarily

1 know exactly in this day and age what the treatment effect
2 of even Penicillin in those patients is right now.

3 DR. WARD: Their comments were for the
4 indications for Group B strep, pneumococci, staphylococci,
5 H. flu, E. coli, enterobacter, and clapsiella [ph.] It
6 didn't sound like anything specifically for children with
7 sickle cell.

8 FDA Review of Cefuroxime

9 Dr. Alan M. Shapiro

10 DR. SHAPIRO: I have to concur with Dr.
11 Alexander and Dr. Wiederman. I think for patients under
12 three months I don't see any benefit. I think for the
13 most part sickle cell kids under three months are most
14 likely normal kids. It is when they are older that they
15 develop the complication base and many of the renal
16 problems.

17 With the kids under three months of age, let's
18 say for the IV form, we are concerned that this drug may
19 not get well into the CNS. So if I was in the case of
20 using this drug for a kid under those circumstances, I
21 would probably stick with a third generation cephalosporin
22 where I feel more comfortable that the drug is getting

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1 into the CNS.

2 **Open Discussion**

3 DR. WARD: Jeff.

4 DR. BLUMER: If we are talking about the oral
5 formulation, I think the one thing that hasn't been
6 mentioned is the oral formulation is the worst tasting
7 oral formulation of an antibiotic in existence.

8 [Laughter.]

9 DR. WARD: That always recommends it highly in
10 pediatrics.

11 [Laughter.]

12 DR. SNODGRASS: Can I make a recommendation that
13 we delist this?

14 DR. WARD: I think everybody gets a chance to
15 vote. Dr. Snodgrass is recommending delisting.

16 Yes, Steve.

17 DR. LAWLESS: I think one of the criteria that
18 you have to mention in terms of, is there any study
19 looking at racial or gender differences in drug
20 metabolism, I mean, if you talk about sickle cell being a
21 specific racial disease. We are not addressing it, but is
22 that one of the underlying reasons; are there any studies

1 that actually address that. This would be the one time
2 that I would think there was a study, this would be the
3 time, because it would show that.

4 DR. WARD: I come from Utah, and we don't take
5 care of many kids with sickle cell.

6 [Laughter.]

7 PARTICIPANT: But you do have your genetic
8 problems.

9 [Laughter.]

10 DR. WARD: We do have our share of recessively
11 inherited disorders.

12 They quote those issues in here, but my
13 recollection of sickle cell was that in the young infant
14 it wasn't a particular problem. They didn't present with
15 asplenia and they didn't have infarctions at that early
16 age. So I think there is a disconnect in this.

17 DR. OVERTURF: Actually, can I?

18 DR. WARD: Yes.

19 DR. OVERTURF: The issue on when splenectomy
20 becomes a problem in sickle cell is a debate. For
21 instance, the Jamaican studies showed that half their
22 deaths from pneumococcal substance occurred before the

1 first year of life.

2 So despite the fact that when you look at the
3 total data on when kids get a splenectomy or have a
4 functional defect, it is a continuum. So some children
5 probably acquire this quite early, but I don't think it
6 makes any difference in terms of this discussion because I
7 think all the comments about this being the worst oral
8 cephalosporin to take in the world are quite germane if
9 you are going to use this for a prophylaxis, as an
10 example.

11 The fact that it really does not have the best
12 of activities against resistant pneumococci or Haemophilus
13 influenza, it makes it a moot point. This is not a drug
14 one should select or would select for prophylaxis in
15 sickle cell, even if you believed any of these other
16 issues were germane.

17 DR. ZAOUTIS: One additional comment to Dr.
18 Overturf. I agree with him about the pneumococcus issue.

19 When you compare the MICs against resistant pneumococci
20 between Amoxicillin, Penicillin, and then Cefuroxime,
21 Cefuroxime is inferior to those agents in terms of the
22 time above the MIC.

1 The second is a paper that was published several
2 years ago in CID looking at risk factors for mortality
3 from pneumococcal sepsis by Victor Yu [ph.] Among the
4 beta-lactams, the only risk factor for increased mortality
5 was the use of Cefuroxime for pneumococcal disease.

6 DR. WARD: Wonderful. Other than that, it has a
7 great therapeutic effect.

8 [Laughter.]

9 DR. WARD: All right. Stan, yes.

10 DR. GROGG: What else needs to be said.

11 [Laughter.]

12 DR. GROGG: It is very expensive, too, so if you
13 are replacing Penicillin --

14 [Laughter.]

15 DR. LASKY: It tastes bad and it is expensive.
16 There you go.

17 DR. GROGG: And it is ineffective.

18 DR. STILES: I was just going to make a comment
19 that has nothing to do with the drug in particular, but
20 more of a generic situation we have gotten ourselves into.

21 Part of what we are doing is talking about
22 places where we actually have good information or

1 reasonably good information and best practices out there
2 for pediatricians. They don't use it and wait.

3 One thing that maybe should be at the end of the
4 whole session is that we ought to feed this back to other
5 groups that ought to be dealing with best practices.

6 DR. WARD: That is a good point.

7 DR. LASKY: I just wanted to also throw out that
8 this is our first time doing this kind of outreach with
9 the NIH institutes, and hopefully, over time, when people
10 respond at the outreach, they will provide more
11 information. It is a little hard to know.

12 Some time was put into this. NIH sent it out to
13 a pediatrician professor at a very good university, and
14 either they didn't put enough information down or they are
15 off base, but this process will have to develop so that we
16 have the information and the full thinking behind it and
17 be able to respond to it.

18 At a minimum, I think after this meeting we
19 could have a conference call just to make sure we are not
20 missing anything on the thinking here, but at least we can
21 respond to these people and say, "Look, we had these
22 people, we talked about it, they didn't see it, and you

1 can come back with more information or move on," that kind
2 of thing.

3 DR. RODRIQUEZ: As a personal participant in the
4 development of Cefuroxime both for the oral and for the
5 IV, I'm sitting here enjoying this.

6 [Laughter.]

7 DR. RODRIQUEZ: We even had adults who
8 volunteered to have their sinuses perforated after
9 Cefuroxime to demonstrate that there was a decrease in the
10 amount of bacteria, including streptococcus pneumonia in
11 the '80s.

12 See, this is the big point. I mean, in other
13 words, we used to talk about Cefaclor before? Okay, that
14 was some time earlier. In other words, the drug had its
15 time, and it is time to move forward.

16 DR. WARD: Thank you, Bill. I thought I was
17 going to have to say something really retracting a
18 negative statement.

19 [Laughter.]

20 DR. WARD: In the discussion so far, I guess I
21 have not seen more unanimity of negative feelings about a
22 drug this morning.

1 DR. RODRIQUEZ: By the way, I used one in a
2 drink to my daughter who had sinusitis. She was better
3 within 24 hours, but I had to pay her quite a bit of money
4 for her to take it.

5 [Laughter.]

6 DR. RODRIQUEZ: By the way, the only being that
7 liked it was my brit dog, who loved it. But I haven't
8 found a kid who likes it yet.

9 PARTICIPANT: And the dog has no sinusitis.

10 DR. RODRIQUEZ: No.

11 DR. WARD: I think on that note, it is time for
12 lunch.

13 [Laughter.]

14 DR. WARD: We will resume around 1:00 p.m.

15 [Lunch recess.]

16 + + +

17

A F T E R N O O N S E S S I O N

[Reconvened 1:01 p.m.]

DR. WARD: So I think we are down to Cephalexin, with Dr. Overturf and Dr. Zaoutis.

Review of Cephalexin**Dr. Gary D. Overturf**

DR. OVERTURF: I think I will not use the computer.

Cephalexin. I was asked [to review] oral and respiratory infections, basically. Actually, a lot of the infections -- [off mic] and streptococcus -- [off mic], which are two respiratory pathogens -- [off mic] indications specifically for all pathogens.

So there is abundant data regarding Cephalexin.

It is a very old drug. It has been used mostly in skin and soft tissue infections, and primarily in treatment of bone and joint infections.

For respiratory and oral infection in general, there is relatively little data, except for some respiratory infections, like pharyngitis, which I will just mention briefly.

Actually, in looking for pharyngitis studies, I

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1 found five randomized control trials, of which, one was a
2 prospective randomized, controlled, blind trial which had
3 about 500 patients -- [off mic] equivalent,
4 microbiologically speaking. It is a relatively recent
5 study.

6 As a result, there is a good deal of safety data
7 also for Cephalexin, but for other respiratory infections
8 other than pharyngitis, there is no data that is really
9 prospective and controlled for such infections like
10 pneumonia, oral infections of any kind that I could find.

11 Obviously, some of the respiratory infections
12 can be of high morbidity or are associated with infections
13 of high morbidity.

14 The other thing was that there are many other
15 agents which are comparable, but with the exception of the
16 bone and joint infections, there has been no empirical
17 trials of any other drug, any of the other cephalosporins,
18 that might be useful.

19 So I gave this a total point of seven, but
20 mostly for relabeling. I don't really think this needs to
21 be relisted. I think the data is available, but much of
22 the data needs to be relisted in the indications, which

1 does include bone and joint infections, but it needs to be
2 expanded to include PK and safety data on larger doses,
3 because the stated dose is still 25 to 50 milligrams. So
4 most of what needs to be done, I think, for Cephalexin is
5 a relabeling based upon available data, which I think is
6 adequate to support it.

7 On the other hand, if one were of the opinion
8 that we needed this drug for respiratory infections other
9 than pharyngitis, it would require a study. Its spectrum
10 of activity is not adequate for most respiratory
11 infections or for infections like sinusitis and other
12 infections in childhood. So that I really don't think it
13 needs to be relisted.

14 The other place where it is used a great deal in
15 pediatrics is for urinary tract infections. It is a
16 useful drug. It does have an indication, although it
17 doesn't say it specifically, in children. I would give it
18 a low priority because the standard dose is -- [off mic] a
19 wide acceptance over many years.

20 So in summary, I really felt that the specific
21 indication we are being asked for of oral infections, I
22 think there are no data, and I don't think there should

1 be. So I wouldn't recommend studying that because, based
2 on spectrum and based on other drugs, it would probably be
3 not suitable for that indication.

4 For labeling, there probably needs to be a
5 change in some of the labeling, just based on available
6 data.

7 DR. WARD: Thank you.

8 **Secondary Review of Cephalexin**

9 **Dr. Theoklis E. Zaoutis**

10 DR. ZAOUTIS: I agree with Dr. Overturf,
11 specifically addressing not the respiratory infections but
12 the oral infections. The task was oral?

13 DR. WARD: I believe it was nominated by the
14 pediatric dentists, actually, so they are, I'm sure,
15 focused on gum and sinusitis.

16 DR. LASKY: If you want me to read what it says,
17 "First-generation cephalosporins are not first
18 choice or even good alternative agents for the
19 management of acute oral infections,
20 particularly because they lack significant
21 activity against oral anaerobic pathogenic
22 microorganisms. However, there are many

1 anecdotal reports of use of this agent in
2 dentistry.

3 "Since the safety and efficacy for this use in
4 children have not been established, the
5 prevalence of these uses of Cephalexin should be
6 assessed, and further reports on its appropriate
7 and inappropriate use should be promulgated."

8 DR. OVERTURF: I think it is another example
9 where a placebo works well for non-existent conditions.

10 DR. WARD: So sort of addressing their comments.

11 [Laughter.]

12 DR. ZAOUTIS: I think the safety and efficacy of
13 the drug has been established in children even of other
14 diseases.

15 They sort of made the statement that I was going
16 to make up front, that oral infections are usually
17 polymicrobial and oral anaerobes are a big part of those
18 infections. Cephalexin has minimal anti-anaerobic
19 activity in contrast to Penicillin and other drugs, so
20 from a drug-drug match, it doesn't seem to be appropriate.

21 I think the cases that have shown resolution have
22 probably been resolved because of the host or other

1 factors.

2 So I actually gave it a three, but that was
3 stretching it.

4 DR. WARD: Okay. So we have a stretched three.

5 FDA will speak to this.

6 Dr. Alexander.

7 DR. J. ALEXANDER: I'm not sure how much more to
8 add to that.

9 [Laughter.]

10 **FDA Review of Cephalexin**

11 **Dr. John Alexander**

12 DR. J. ALEXANDER: I realize that Cephalexin is
13 a fairly old drug, and so many of the indications and the
14 way that the label reads is a product of the fact that it
15 is older even than Cefuroxime. The way that the label is
16 written, it actually has dosing recommendations on the
17 dose that is meant to be given for children for treatment
18 of the indications that are listed.

19 I accept the comments about the fact that now
20 much higher doses of Cephalexin are being recommended for
21 bone and joint infections and that that is still sort of
22 an off-label use, but I think that that is potentially a

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1 use that could be sort of studied separately where you get
2 information on PK penetration into bony tissues with a
3 higher dose in safety, and that would probably be
4 sufficient for putting in more information on the label
5 about that sort of use.

6 When it comes to oral infection, I don't really
7 see that there is a great need for this, and I agree that
8 the idea of its activity against anaerobic bacteria, which
9 are what you would be concerned about with oral
10 infections, doesn't make it a particularly good choice for
11 that.

12 **Open Discussion**

13 DR. SACHS: The only thing that I was going to
14 add was that this is on the list for drugs that should be
15 recommended in SBE prophylaxis for Penicillin-allergic.
16 The alternatives are Clindamycin, Clarithromycin, and
17 Zithromax. Of the group, it is pretty much the best
18 tolerated and least expensive. So my question was whether
19 or not SBE prophylaxis would really be a reasonable
20 indication.

21 I will say I was surprised at the nomination,
22 particularly when you look at the approved spectrum of

1 organisms that it helps. The microbiology didn't seem to
2 match, but at least as far as SBE prophylaxis, I think it
3 is actually not an unreasonable indication to look at.

4 DR. OVERTURF: Actually, you open a real can of
5 worms if you are going to open the whole issue of SBE
6 prophylaxis, because virtually none of the drugs that are
7 actually recommended for SBE prophylaxis are based upon
8 actual data that suggest that you even can change the
9 instance of bacteremia post procedure. They are based
10 upon activity and likelihood that their PK and PD and the
11 antimicrobial spectrum that they are treating will be
12 adequate to maintain a low count or eliminate bacteremia,
13 but there is no data that that is true.

14 So I think you are right, it is a reasonable
15 drug. I would like to make a comment about this issue of
16 the septic arthritis and osteomyelitis. That is a
17 prescription that I have to write about two or three times
18 a week because PEDEs ID [ph] people take care of that
19 condition almost exclusively these days. At least once a
20 week, I get a call from a pharmacist who looks this up and
21 won't fill the prescription because the label is 25 to 50
22 milligrams per kilogram.

1 So if it is studied and felt that there is
2 adequate data to support the safety of that, then I think
3 it ought to be on the label, because it would actually
4 save me at least one telephone call a week.

5 DR. ZAOUTIS: Two points, one regarding the SBE
6 prophylaxis. I was recently informed that the AAHA, when
7 they meet again, will be actually changing those
8 recommendations for prophylaxis to minimize antibiotic use
9 in the prevention of SBE prophylaxis significantly. So I
10 think the recommendations are going to be change and there
11 will be minimal antibiotic use post dental procedures for
12 SBE prophylaxis, although I don't have that formal
13 information.

14 DR. WARD: So we can be in front of that curve.

15 John, could you comment about whether the label
16 specifically indicates its ineffectiveness for anaerobes?

17 DR. J. ALEXANDER: No, not usually. I mean,
18 what usually happens is that we list the organisms for
19 which there is known activity related to the particular
20 indication that they have. So the organism goes into the
21 list if the drug shows that it has activity against that
22 organism and that it is used in a specific indication in

1 which that microorganism is known.

2 DR. WARD: So if I were a dentist and I knew
3 that there were anaerobes in the mouth I wanted to cover
4 and I knew what anaerobes those were, I wouldn't find it
5 in the label, but I wouldn't specifically say "does not
6 cover anaerobes."

7 DR. SACHS: It does say it is not active against
8 anaerobe coccus and that there is really no activity
9 against asinadobacter [ph.]

10 DR. RODRIQUEZ: An interesting thing is that in
11 a manual for dentists it says "third drug of choice for
12 oral -- [off mic], for acute dental infection of -- [off
13 mic] gingivitis, periodontal abscess, and periodontitis."
14 They give it in combination for both children and adults
15 with different dosage regimens. So again, another area
16 that we need to educate.

17 DR. OVERTURF: Do we try to educate through
18 study? I think we need to educate through education.

19 DR. RODRIQUEZ: This drug is pretty well known
20 in the area of anaerobic infections in the antimicrobial
21 therapy guide for dentists. It is an article from 1999,
22 and he put it down as the third option.

1 DR. WARD: Yes, Stan.

2 DR. GROGG: Just a comment. It is cheap and it
3 tastes good, versus Cefuroxime.

4 [Laughter.]

5 DR. GROGG: But in this day and age of resistant
6 and community environment and so on, resistant staph, at
7 least in my area of the country where about 50 percent are
8 resistant to first generation cephalosporins, I think it
9 needs stronger labeling in the indications. Right now, it
10 lists susceptible strains of this microorganisms, and they
11 include Haemophilus and staph and M. catarrhalis, which it
12 really doesn't have any effect at all.

13 I think I would go along with that it needs to
14 not be researched further but relabeled.

15 DR. OVERTURF: I would agree with that. I
16 actually had a point -- I had it in my write-up, but I
17 didn't mention it at the podium -- that in most localities
18 now, particularly skin and soft tissues infections, well
19 over 50 percent of them are community acquired MRSA, and
20 this would not be an agent that would be active.

21 DR. WARD: Can that be taken back, then? We
22 would recommend relabeling of it based on published

1 information.

2 All right. Place your votes for it.

3 Jeff, do you want to talk about Acyclovir for
4 hepatic infections?

5 DR. BLUMER: Yes, that is like talking about
6 Penicillin for infection.

7 [Laughter.]

8 **Review of Acyclovir**

9 **Dr. Jeffrey Blumer**

10 DR. BLUMER: So Acyclovir is an antiviral agent
11 that works through intracellular mechanisms of
12 phosphorylation. The charge to look at hepatic infections
13 wasn't entirely clear because the Acyclovir package label
14 that was given was for the clinical formulation, and many
15 of the references were for gingival stomatitis or for
16 prophylaxis.

17 But overall, I think if you look at this for the
18 one pediatric label indication, I think there was adequate
19 and well controlled trials done for herpes simplex
20 encephalitis in the newborn, for herpes infections in the
21 newborn, and the carryover with herpes simplex
22 encephalitis both in children and adults.

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1 So I think that there is adequate
2 pharmacokinetic data, not that the pharmacokinetic data,
3 once again, in this particular area is all that useful
4 because the activity of the drug is intracellular and in
5 many respects the Acyclovir requires metabolism in order
6 to be activated.

7 So that, I guess I looked at the data that was
8 there. I didn't think that there would be much gained by
9 looking at Acyclovir in a variety of these different
10 indications when the parental drugs specifically were
11 dealing with serious and life-threatening infections. The
12 drug has been documented to work and work in our most
13 vulnerable populations.

14 So I felt that while it is an important problem,
15 it is a life-threatening problem, I think the drug has
16 been demonstrated to work, and I didn't think that we
17 would learn much more by doing more long-term or well-
18 controlled studies of either the pharmacokinetics or
19 efficacy.

20 The safety profile is, the risk benefits seem to
21 be well defined and well worked out, and so, again, there
22 didn't seem to be much in a way that would be gained from

1 further safety evaluations.

2 DR. WARD: Is the label currently up to date
3 with correct dosing?

4 DR. BLUMER: No, no, no.

5 **Secondary Review of Acyclovir**

6 **Dr. Gary D. Overturf**

7 DR. OVERTURF: That was actually my point. The
8 current dosing is 20 milligrams per kilogram qid 8 hours,
9 so it is over twice the label dose, which I think is 10
10 milligrams per kilogram qid 8 hours.

11 I agree that there are many less well
12 established treatment use of Acyclovir both in the oral
13 and the IV formulation and primarily for prophylaxis in
14 children for current non-genital infections, primarily
15 with type I herpes and also some what I would have to call
16 hepatic associated conditions like arigamulitformine [ph]
17 and Bell's palsy, in which children are often treated for
18 those two conditions with little or no data.

19 But again, since it is not labeled for that, to
20 me, I don't think I would put those in the label. I would
21 not encourage their use for conditions that I think are
22 poorly established as links with hepatic infection.

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1 I think there does need to be updating of the
2 labeling of the dose for neonatal herpes.

3 DR. LASKY: I just wanted to make two points,
4 and we will have to deal with this at the end. I think if
5 NICHD is going to take literature and use it as a means
6 for asking for a label change without doing additional
7 study, it still will have to be on the priority list. So
8 we may have to add a category that we don't see the need
9 for clinical studies but we do see the need for studies or
10 efforts leading to relabeling. I'm not exactly sure,
11 because we haven't really worked this issue out.

12 Second, Gary, this is a nice example, because we
13 have been wondering how these drugs and conditions have
14 gotten on the list. We have this letter that you signed
15 here from the Pediatric Infectious Disease Society.

16 [Laughter.]

17 DR. OVERTURF: I actually signed it, but I
18 actually wrote it. I can't remember what I said.

19 [Laughter.]

20 DR. LASKY: Yes, I was recognizing some of your
21 comments. So you at least need to confess to that.

22 [Laughter.]

1 DR. WARD: Do you want to comment from the FDA?

2 **FDA Review of Acyclovir**

3 **Dr. Melisse Baylor**

4 DR. BAYLOR: My name is Melisse Baylor, and I'm
5 a reviewer in the Antiviral Division. When Acyclovir was
6 approved for IV for treatment of neonatal herpes
7 encephalitis back in '98 I think it was, in June, they had
8 had the kind of big study that was done by the Colebbeter
9 [ph] Antiviral Study Group. It had been published in the
10 New England Journal, and they had that data to go on.

11 They knew the second study from the CASG was
12 going on, which was the 45 versus 60. They had a little
13 bit of preliminary data for review, and they looked at it,
14 and they got no safety data from it. It looked like
15 mortality and morbidity were going to be lower, but they
16 had very little data.

17 So what they comment on is that they had
18 encouraged the patent holder at that time to submit that
19 data and justify the higher dose. After that, in fact,
20 they were also asked to submit some data for a higher
21 dose, and that data was never submitted.

22 So the FDA did try to get the higher dose data,

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1 but the sponsor chose not to. It actually says in their
2 review -- which is FOI-able, so I can say -- that the
3 applicant preferred the 10-per-kilo-per-dose rate to be in
4 the label.

5 So I think that we figured it was one of those
6 things where everybody was comfortable using it, it was
7 happy, but they didn't have to worry about it and didn't
8 have to give us any money to review a new supplement, and
9 they could move on. It saved costs.

10 **Open Discussion**

11 DR. OVERTURF: In the redbook, it is listed as
12 60. I know, because I helped write that.

13 So at least within the pediatric infectious
14 disease community, that has been the accepted dose, and I
15 think within the neonatal community as well.

16 DR. BAYLOR: That is one of the reasons that we
17 haven't pushed it lately. We felt like everybody knows
18 how to use it. It is accepted to use it. It is in the
19 redbook. Yes, the label is out of date.

20 DR. WARD: The reason to discuss this out loud,
21 I think then in that situation on our ballots you can go
22 ahead and write in something about that, and we will let

1 the NIH and the FDA figure out how they are going to
2 approach the company about this.

3 I personally and philosophically object to
4 having incorrect data there, especially if it may be
5 inadequate and which makes it dangerous.

6 DR. BAYLOR: Well, there was a justification in
7 the review of leaving it at 30, and they did say that they
8 were never studied head to head. The 60 versus the 30
9 were never studied head to head, that the disease itself
10 had changed, and there was an article saying how HSV
11 encephalitis had changed a little bit during the time, and
12 they felt like there was a little bit of difference in the
13 populations. They felt like they couldn't compare them,
14 and with the company objecting to going to it, they felt
15 like they were comfortable leaving it at that. So they
16 did realize that.

17 I think that if it is something that you can do
18 from the literature review, from the article that was
19 published in multiple forms, to update the label, you
20 could do it. Unfortunately, in the CASG study, there were
21 a smaller number at the intermediate dose at 45, and
22 almost all the PK was done at the 45. So we could update

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1 the label to reflect more the pharmacology results from
2 the 45, because it doesn't have that in the efficacy from
3 the 45 and 60.

4 DR. OVERTURF: One of the problems with changing
5 the labels, particularly, is this area is not static. For
6 instance, the duration of therapy still has not been
7 defined. They are still gathering data for the 21-day
8 regimen as opposed to the 14-day regimen, which has a
9 different outcome measure which is primarily the instance
10 of relapse in disease after treatment.

11 So it is problematic. It is different than the
12 Cephalexin that we just mentioned. That data was
13 established a long time ago and hasn't changed now in 20
14 years, but this is still a static area where there is not
15 a complete revolution. I don't know how to handle that.

16 DR. BAYLOR: I think it is doable. The question
17 is, can we do it with data from the literature without
18 companies cooperating. It is certainly doable to write in
19 the label that people who get treated from this length of
20 time to this length of time and the ideal treatment to
21 prevent relapse.

22 So we can do it. It is just we have never had a

1 cooperative company.

2 DR. WARD: Is the data about 21 versus 14 robust
3 enough that we can expect it to be definitive?

4 DR. OVERTURF: I would have to ask Rich Woodley
5 [ph.] I don't know.

6 DR. LASKY: This also raises some issues that we
7 have been struggling with, whether it is important to have
8 labeling changes or it is important to have an increase in
9 knowledge and information. Of course, they are both
10 important, but we do get measured and evaluated by
11 Congress with respect to numbers of label changes.

12 That doesn't mean we have to put that ahead of
13 actually getting new knowledge, but I just wanted to lay
14 that out there as a reality and something that we have to
15 deal with to some degree.

16 So if there is a reason to make a labeling
17 change and it isn't that costly, that is something that
18 Congress wanted to see accomplished, and that is actually
19 almost why not go ahead and do it if it is not that
20 difficult to do. I think the issue of what published data
21 meet the criteria is going to be addressed somewhat by our
22 contractors who could be working on the systematic

1 literature reviews and meta-analyses. It is really an
2 unpaved, unregulated area, but I think we have the
3 resources there to actually do that.

4 DR. WARD: I think that is a very important
5 collaboration between the FDA review officers and NIH to
6 determine what serves public health the most.

7 DR. LASKY: Well, it also doesn't take funds
8 away from the clinical trials, so it is not actually an
9 either/or kind of thing, because the labeling changes will
10 cost some money both from a literature assessment and
11 regulatory process, but it won't cost the kind of money
12 that a clinical trial will. So it will not take away from
13 the clinical studies that we can do.

14 DR. WARD: Yes, Jeff.

15 DR. BLUMER: I was just wondering, is there a
16 provision within the FDA to add to labels based on expert
17 opinion? Because this is going to be true for all the
18 anti-infectives, whatever class they are in. As Gary
19 points out, these things never are static.

20 Yet whether or not you find data in the
21 literature that would satisfy your review criteria, if you
22 took all the pediatric infectious disease specialists in

1 the country and asked them, "What dose of Acyclovir do you
2 use?", I think you would have fair unanimity at this point
3 in time.

4 DR. OVERTURF: It has been my practice to never
5 get more than three infectious disease people together at
6 once.

7 [Laughter.]

8 DR. BAYLOR: Three is too many.

9 [Laughter.]

10 DR. OVERTURF: You probably won't get the same
11 answer.

12 [Laughter.]

13 DR. OVERTURF: But I agree.

14 DR. LASKY: I don't think, from our end, that we
15 are talking about expert opinion. We are talking about
16 credible meta-analyses.

17 DR. BLUMER: I understand that, but you may not
18 find it, and yet the literature may still not be
19 reflecting what is now standard practice. I think the
20 bone and joint infection treatment with Sublexim [ph] is a
21 good example of that. You may or may not find enough
22 compelling data in the literature to support that.

1 DR. BAYLOR: There are provisions in the
2 regulation that allow literature to be used for updating
3 labels. So that is not a problem. The thing that I don't
4 know -- maybe John can shed some light on this -- if the
5 company is not very excited about it, can we still do
6 that.

7 DR. BLUMER: That is going to be true for this
8 entire process.

9 DR. BAYLOR: So how to finesse that part of it,
10 I don't know.

11 DR. J. ALEXANDER: I think that that is going to
12 be part of the issue. When we go through this in terms of
13 getting new information from this off-patent process, I
14 think that the way that it is going to end up working --
15 and maybe some of the PEDE's people can correct me if I'm
16 wrong -- is that we are going to sort of review this
17 information that NIH collects from their studies, and
18 based on that, we would end up publishing a Federal
19 Register notice that tells companies to "Come on in with
20 your drug and relabel it this way."

21 That is going to be in part difficult to do if a
22 company is just going to decide, "Well, I'm just going to

1 drag my feet. I'm not going to do that because I'm not
2 particularly interested in having that information in the
3 label the way that it is presented.

4 Going back to the other question about the data
5 in the literature, we do have to be very careful that we
6 aren't doing things based on solely the opinion of
7 experts, because FDA has gotten burned by that in the
8 past. So we are supposed to be basing things on data that
9 is supplied to us.

10 We do have instances where we have done
11 literature-based NDAs, literature-based reviews of
12 particular uses, and then gone ahead and labeled that.
13 That has usually been with the cooperation of companies,
14 but we have to be careful about the quality of the data
15 that we get from being able to look at those literature
16 articles, and oftentimes have had to go back and actually
17 ask for the source data on which those articles were based
18 in order to provide us with enough data that we could
19 review to say that a labeling change is justified.

20 DR. LASKY: I think we see it exactly the same
21 way, or that is my vision in terms of using the
22 literature. I think in terms of describing practice, I

1 don't think we could consider a description of practice as
2 a demonstration of efficacy and safety.

3 So the fact that every pediatrician or every
4 whatever in the country is prescribing at a certain dose
5 doesn't really demonstrate that it is the best dose. It
6 is an important piece of information, but we would want to
7 go beyond that.

8 DR. WARD: Lisa, go ahead.

9 DR. MATHIS: I just wanted to go ahead and
10 clarify that the BPCA actually does have a provision where
11 the sponsors must incorporate this information within a
12 certain time frame. If they don't agree to do so, we take
13 them to advisory committee. So we do have a mechanism in
14 order to get this information into labeling.

15 DR. WARD: It would seem to me that there is the
16 force to make this happen if there is adequate literature
17 to support that dosing.

18 So what I would like would be that, for
19 Acyclovir, if you want to recommend that relabeling be
20 carried out to reflect the current level of information,
21 write that into the side or somewhere on your form. Then
22 we will at least have the opinion of this group in support

1 of that.

2 A wonderful drug, Amantadine for influenza.

3 Dr. Meythaler.

4 **Review of Amantadine**

5 **Dr. Jay M. Meythaler**

6 [PowerPoint presentation.]

7 DR. MEYTHALER: Amantadine is a small molecule.

8 It has been around for a long time. The drug was
9 developed originally as an antiviral agent. It is not
10 recommended as a substitute for influenza vaccine. I want
11 to point that out this year with the vaccine shortage.

12 The dose has generally been five milligrams per
13 kilogram for kids older than 10. It tends to vary between
14 4.4 to 8.8 milligrams per kilogram for children. It is an
15 approved use by the FDA, but the studies weren't so
16 motivated. It was more a pharmacokinetic study in kids,
17 where most of the research was really done in adults and
18 in isolates. It is generally used for influenza A. It is
19 not useful in influenza B.

20 I think these are just the kinetics. I'm not
21 sure that anybody really needs to see all that.

22 It is a stable drug. It comes in tablets,

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1 capsules, and a syrup. The last count I had -- actually,
2 I just looked it up on the website -- it is 10
3 manufacturers that are active in the United States, some
4 of which produce a syrup and elixir. So it makes it
5 available for kids.

6 The interesting point is, there is a large
7 market for this medication, obviously. That is the
8 interesting point.

9 Mechanism of action. As I said, its antiviral
10 action is not clear. It appears to prevent release of
11 infectious viral nucleic acid into the host, interfering
12 with the function of the -- [off mic] protein. In certain
13 cases, Amantadine is also known to prevent virus assembly
14 during virus replication. As I said, it is really only
15 activated in influenza A, not B. The subtypes are H1N1,
16 H2N2, and H3N2, which are generally other versions.

17 An interesting point [off mic] in kids -- I have
18 to bring this up because [off mic] -- is that Amantadine's
19 biggest use is probably in [off mic].

20 Amantadine -- [off mic] has effects similar to
21 [off mic] which, by the way, is nothing more than a
22 dimethyl ester of Amantadine. Actually, in vivo and in

1 vitro research indicates a possible blood-brain barrier at
2 similar concentrations. They attach to all the -- [off
3 mic] similarly.

4 For the summary, in my opinion, the FDA [off
5 mic] the United States -- [off mic] \$1 billion. The
6 Europeans don't allow -- [off mic] versus Amantadine.

7 It is also related to another drug we are going
8 to review called Rimantadine, which has much less
9 dopaminergic effects.

10 The side effects of Amantadine are generally
11 also related to the CNS suspects, and it is profound.
12 However, it has been reported to improve alertness and
13 facilitate neurologic recovery in patients with brain
14 dysfunction of various kinds. There are also similar
15 points in review -- [off mic] patients both acquired and
16 progressive, like in Alzheimer's disease, Parkinson's, or
17 even traumatic brain injury.

18 Amantadine is a tricyclic. As I said, it
19 affects the reuptake of dopamine. It has some weak
20 serotonergic effects and weak NMDA effects.

21 Now, the drug is predominantly metabolized in
22 the kidney. It has advantages over Amantadine, and it

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1 does [off mic] liver function. It is pretty much linear
2 pharmacokinetics. That is an advantage in this situation.

3 It distributes pretty evenly through the body.
4 As I said, 20 milligrams through the day of Amantadine in
5 an adult will give you the same CNS concentration as about
6 40 milligrams of Amantadine, which [off mic] doses.

7 Side effects are incredible: acute psychosis,
8 disorientation, nightmares very frequent. If you have
9 ever taken Amantadine for [off mic] prophylaxis action. I
10 did once about six years ago. The nightmares are real.
11 It is incredible: hallucinations, behavioral disorder, CNS
12 depression, dystonia, and uro-endocrine effects,
13 particularly SIAVH.

14 [Off mic] -- pure anti-epileptic effects. I
15 only cited pediatric references. There are also some
16 adult references. High doses will of course, because
17 adult [off mic] threshold.

18 Parkinson's disease in adults. It has an
19 indication on Parkinson's disease -- [off mic]. It also
20 has an indication in adults for drug-induced reactions --
21 [off mic] off-label, usually.

22 These are some of the off-label uses it has

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1 brought in pediatrics [off mic] this drug in the United
2 States is used for CNS depression. The biggest in this
3 [off mic] is brain injury. Based on a number of studies
4 that have been coming out, there are about four open-label
5 and one randomized control equivalent to a level 2 trial
6 that has been done on the drug, and now there is a multi-
7 center trial, funded by NIDA for the next three years, in
8 the United States to see whether it really does enhance
9 recovery from coma.

10 So this drug is being used hugely. I just came
11 from Neural Trauma. There is a lot of research being done
12 on this drug, partly because -- [off mic]. So they want
13 to go to Amantadine because it is cheaper.

14 These are all the other indications it is being
15 used for. It does have some technical effects in the
16 liver, too, for hepatitis C. It is being used in adults,
17 and there are questions about whether it is being used in
18 kids.

19 Pharmacokinetics are well known to be short-term
20 in children. They are not that much different than adult.

21 The problem is that it has not been studied in all these
22 other diseases neurologically it is being used in, and --

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1 [off mic] has been used for over 12 weeks, now two weeks.

2 This is one issue.

3 The pharmacology kinetics and side effects of
4 long-term use in children has not been well established.
5 The interesting point is that it is rapidly falling across
6 -- [off mic] malignancy, which is frequently not
7 recognized because of its dopamine effects.

8 Traumatic injury is the leading cause of
9 disability in children right now, and in adults, actually,
10 according to the CDC. It is not stroke, because its
11 prevalence is so much greater.

12 The issue is, is the off-label more than it is.

13 If I had to score this, I would give it a four because of
14 influenza. I would give it a six for taking a look at the
15 short-term issues. It clearly hasn't been looked at for
16 the long-term issues. It is not as high a score as some
17 people would be giving it. As I said, it has been used in
18 adult trials, recently in a randomized trial.

19 DR. WARD: Wayne.

20 **Secondary Review of Amantadine**

21 **Dr. Wayne R. Snodgrass**

22 DR. SNODGRASS: I have very little to add,

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1 except that long-term use of agents that affect the
2 dopaminergic pathway can lead to tardive dyskinesia, which
3 is irreversible. I am aware of cases with Metaclopramide
4 [ph] as an example, which we don't think about that.

5 So I think the long-term issues clearly have to
6 be studied if you are going to use this type of an agent.

7 DR. WARD: Let's hear from the FDA, then. I
8 think the FDA needs to address this issue of the totally
9 different indication than that listed.

10 **FDA Review of Amantadine**

11 **Dr. Melisse Baylor**

12 DR. BAYLOR: The antiviral edition typically
13 reviews it only for its influenza use.

14 [Laughter.]

15 DR. BAYLOR: So I'm going to take that out. I
16 will say, as far as influenza, we are not real interested
17 in any more studies with this drug.

18 After listening to that, I think it needs more
19 neurological studies.

20 **Open Discussion**

21 DR. WARD: Jeff.

22 DR. BLUMER: I guess, going back, personally, I

1 agree with both parties. I think we have missed the mark
2 here totally.

3 Going back to influenza, this is an interesting
4 scenario, because even though we do know the
5 pharmacokinetics in children, once again, the
6 pharmacokinetics were performed, if you will, in a sterile
7 environment. So they have been related to nothing.

8 DR. SNODGRASS: That's true.

9 DR. BLUMER: If you go back even through the
10 short-term use of Amantadine in influenza infections, I
11 have no idea whether any of those adverse events that
12 occur with short-term use are concentrated in the label.
13 I mean, we have something that is relatively cheap and is
14 widely used. Can we more safely use this drug if we knew
15 of a relationship between the pharmacokinetics and the
16 pharmacodynamics, specifically safety, not efficacy.

17 So there may be some reason to look at it in
18 that regard, but I agree with you wholeheartedly. The
19 overwhelming need is to now look at this as a CNS actor.

20 DR. LASKY: My conclusions that I'm coming to
21 are that next year we are not going to have an outreach
22 process because I hate to tell you which agency suggested

1 this drug. But we did this outreach and, I don't know, we
2 are going to have to discuss it tomorrow and see how we
3 can make it better. There is either a disconnect between
4 all these different agencies and the group of experts
5 here, or there is information that hasn't been explained.

6 The Office of the Director of the National
7 Center for Infectious Disease at the Centers for Disease
8 Control nominated both Amantadine and Rimantadine, and I
9 will just read to you what they sent. They have several
10 pages here, but they give a little background on what
11 Amantadine is, what we have heard so far.

12 They say,

13 "Data Needs. Further randomized double-blinded
14 placebo-controlled clinical trials of Amantadine
15 for treatment in chemoprophylaxis of influenza A
16 virus infection is needed, especially to examine
17 the potential to reduce influenza A among
18 healthy and chronically ill children.

19 Randomized double-blinded controlled clinical
20 trials comparing Amantadine with other antiviral
21 medications and placebo when used for treatment
22 and chemoprophylaxis of influenza A are also

1 needed.

2 "There are limited pediatric data on the
3 efficacy and adverse effects of Amantadine when
4 used for treatment. More data are needed about
5 potential gastrointestinal and central nervous
6 system side effects of Amantadine when used for
7 treatment of influenza A among children.

8 "There are no data on the efficacy, adverse
9 effects, and pharmacokinetics of Amantadine for
10 treatment of chemoprophylaxis of influenza A in
11 children under one year old."

12 It is kind of perplexing to me. It is going to
13 be something we are going to have to mull over. Something
14 is not connecting between our different institutes,
15 agencies, and groups.

16 What they said for Rimantadine is almost the
17 same. When we get to it, I will read that as well.

18 DR. SHAPIRO: I would like to make a comment.
19 This was an issue that Dr. Baylor and I had talked about,
20 was that we have a hole for those under one year of age.
21 Basically, Amantadine is approved for the use of those
22 older than one year of age, and so is, also, Tamivir [ph],

1 which is a neuromidase inhibitor which affects both
2 influenza A and influenza B. You are using them in kids
3 that are older rather than those under one year of age who
4 have the highest morbidity and mortality due to influenza.

5 At this point, because of the safety signal that
6 was reported out generally about, also, Tamivir, we have
7 no agents to use for those under one year of age. It is
8 not clear in talking with the Antiviral Division whether
9 either Rimantadine or Amantadine would really fit this
10 group because, number one, we were worried about
11 Amantadine and its toxicity, and Rimantadine has really
12 shown most of its efficacy for prophylaxis rather than
13 treatment.

14 I think we have a therapeutic call that we need
15 to address, but I'm not sure that these two agents are
16 going to do it.

17 DR. ZITO: I was just going to make a comment in
18 response to Dr. Lasky that it might be useful to look at
19 the utilization data in terms of the diagnoses and so on
20 so that you could make a case that utilization isn't there
21 and that would sort of end the story.

22 DR. BAYLOR: Just to kind of reiterate, the

1 Review Division feels like we have more specific drugs now
2 with fewer side effects, easier to tolerate, and active
3 against A and B.

4 DR. MEYTHALER: This is more of an off-label
5 issue. I will tell you, I have run past the pharmacies at
6 a couple of children's hospitals as well as our adult
7 pharmacies. This drug is not being used for an antiviral
8 very much at all. In the adult population, it is over 80
9 percent it is being used in CNS, and in pediatric, it is
10 over 50 at least, I safely can say. It is all off-label
11 now.

12 There is a big market. There are 10
13 manufacturers out there. They are obviously selling it.

14 DR. LASKY: Well, I think this shows that we do
15 need to find out. If it is being used in kids under one,
16 we aren't going to have the conditions associated with the
17 drug use data. We haven't put that completely together.

18 The CDC statement was a bit longer, and I didn't
19 read it. They said during the 2003-04 influenza season in
20 the U.S. there were 142 pediatric deaths with laboratory
21 confirmation of influenza reported to CDC. So it doesn't
22 have the ages there, and it doesn't have a rate.

1 I think it is safe to say that influenza affects
2 the under-ones and affects mortality, but we don't know if
3 Amantadine is being used to treat it.

4 DR. BAYLOR: Interestingly enough, in the MMWR,
5 those influenza deaths were primarily in teenagers. The
6 reason was really unclear whether they didn't receive
7 treatment early or what happened, but they weren't the
8 typical population that you would expect of influenza
9 deaths, being small children, ex-preemies, or BPD. It was
10 very much a surprise.

11 I can't address how much Amantadine or
12 Rimantadine were used last year during the outbreak. I
13 know that our Drug Shortage people worked with the
14 influenza companies to make sure they got as much drug as
15 they could.

16 DR. LAWLESS: Two things, actually, may help
17 here. You were reading the rationale behind some of these
18 reasons. Having some of the rationale behind it, not just
19 saying, "We think these are the ones to be studied."
20 There are certain risk data that people are saying is the
21 justification we are putting forward on this as far as
22 there were 1,000 kids who died last year, or something.

1 That adds a little bit of a different flavor to some of
2 the review and what we are doing with it.

3 The other thing is just a more editorial
4 comment. I don't know how everyone else feels, but having
5 prescriptions without real indications of why someone is
6 writing a prescription, I think there may be some loss on
7 that. I think the idea of maybe, perhaps, from an FDA
8 standpoint or something else -- I know in the Medicare
9 world they do this -- is, you have to put an indication of
10 why you are using a drug so you have a better idea of what
11 the uses really are. That is pretty cheap.

12 DR. WARD: Dr. Pursley.

13 DR. PURSLEY: First, what is troubling is this
14 gap where the vaccination isn't available to infants until
15 six months. Although there is global vaccination for kids
16 between six and 23 months, what do we do for those kids
17 who are at greatest risk who are less than six months, and
18 what do we use in the meantime.

19 DR. BAYLOR: Oh, there is a huge need. I agree
20 totally. There is a huge need for the less-than-one-year-
21 old. Our problem with the questionable efficacy of
22 Rimantadine, there is not the strongest evidence to

1 approve it, and it actually was pretty much equal to
2 Tylenol in treatment studies. The CNS toxicity was
3 borderline efficacy for Amantadine, which makes us
4 uncomfortable identifying either of those as the agent to
5 go for.

6 Then we are left with two more drugs that are
7 approved right now for the A and B, which are the
8 Osotनाविर and the Zanamivir. Osotनाविर has some
9 troubling preclinical data, the animal data, which has
10 been made public in the "Dear Healthcare Provider" letter,
11 where very high doses that were much higher than you
12 should see in real humans, they had some CNS toxicity.

13 As the FDA, we can't really force them to study
14 at lower doses in animals or in children, and I don't
15 think that too many parents would be excited about the
16 informed consent.

17 Zanamivir is our last choice, and frankly, it is
18 being used so little right now that even though there are
19 nebulizers and intravenous formulations that have been
20 studied through the CASG, it is being used so little that
21 the sponsor is really reluctant to put any more money into
22 its development.

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1 So we are in trouble. There is a huge need. I
2 just wish somebody would make a good drug.

3 DR. PURSLEY: One of the problems, of course, is
4 the ability to make the diagnosis and quite a bit of
5 inference about respiratory disease in the first couple
6 years of life is primarily due to respiratory syncytial
7 virus.

8 I think it would be a difficult thing to study,
9 but maybe there are some opportunities for it, because I
10 understand that as of this month there is mandatory
11 surveillance data being sought for influenza in kids. Is
12 that true?

13 DR. OVERTURF: Yes. In most states now, at
14 least deaths from influenza are reportable, and in some
15 other states, hospitalization of children with documented
16 influenza are reportable as well.

17 DR. ZAOUTIS: Tami's comment about at least
18 reading the list of gaps in knowledge, would this be one
19 where a systematic review of the literature trying to
20 address those specific questions, bringing the two sides,
21 bringing the gaps closer together?

22 DR. LASKY: Actually, this is one that from our

1 first look that we can't do from the literature because
2 when we looked at the Metaworks review, although there are
3 a lot of studies on Amantadine, there were only, I think,
4 two on influenza. That is really not enough to do a meta-
5 analysis, unless they are just outstanding studies, which
6 I don't think they were.

7 So we tried to keep this group confined to ones
8 where the literature was a little bit smaller. The ones
9 with a large volume of literature we culled out before
10 handing this group to you. So we cannot use the
11 literature for this.

12 DR. RODRIQUEZ: I just had a question in terms
13 of antivirals for influenza. I thought that Ribavirin had
14 activity, even though it is still a pain in the neck when
15 it has to be given. Essentially, if the person is sick
16 enough to be in the hospital, could we offer that
17 preparation?

18 DR. BAYLOR: Right. Ribavirin has activity
19 against everything in vitro.

20 DR. RODRIQUEZ: No, there is in vivo data,
21 actually, in the Journal of Pediatrics. There was almost
22 a 36-hour difference in fever compared to the control.

1 DR. WARD: So, when you are in vitro, it is
2 terrific.

3 Let me suggest this. The issue had to do with
4 interest in its study for influenza. That is really the
5 question that is on the table. So vote with respect to
6 that. If you feel like we should bring it back to the
7 Neurology Division -- Dr. Sherman is gone right now, I
8 think, when I looked around -- we can write that in and we
9 can at least express ourselves about traumatic brain
10 injury. It sounds like this is a brand new area. Maybe
11 it is not so new, but at least new to me as a
12 neonatologist. That can move forward through the process.

13 But today, I think we need to vote with respect to
14 influenza.

15 Yes.

16 PARTICIPANT: Can we write in also the need for
17 Oseltamivir or some other drug to be studied in the first
18 year of life?

19 DR. WARD: Yes.

20 DR. LASKY: Please do.

21 DR. WARD: Dr. Pursley, should we talk about
22 Rimantadine?

1 DR. PURSLEY: I think I will avoid going to the
2 podium. That will save everybody some time.

3 **Review 2: Off-Patent Drugs**

4 **Review of Rimantadine**

5 **Dr. DeWayne M. Pursley**

6 DR. PURSLEY: This should be pretty quick and
7 easy here, because there doesn't appear to be the extra
8 respiratory indications that Amantadine has had. It has
9 been more limited in that it is not recommended for a
10 prophylaxis in additional treatment.

11 The good news is that it should be a pretty easy
12 meta study because, from what I can gather, there was only
13 one trial of 37 patients done by Carolyn Breeze Hall [ph]
14 that suggested that there was any efficacy to begin with.

15 So I think that what you heard for Amantadine
16 you can assert as well for Rimantadine.

17 **FDA Review of Rimantadine**

18 **Dr. Melisse Baylor**

19 DR. BAYLOR: Interestingly enough, on the FDA
20 analysis of Dr. Hall's review, Tylenol and Rimantadine
21 were equal. It happened that on day 2 Rimantadine was
22 slightly better. By day 5, Tylenol did better and

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1 Rimantadine had built resistance and 41 percent bounced
2 back with more symptoms. So they approved it anyway, but
3 I wasn't around. What can I say.

4 DR. WARD: Two votes for Acetaminophen.

5 [Laughter.]

6 **Open Discussion**

7 DR. WARD: Again, let's vote on this with
8 respect to influenza, as indicated on the ballot.

9 DR. LASKY: I'm not sure; are you saying that
10 these aren't effective for influenza or haven't been
11 demonstrated to be efficacious?

12 DR. BAYLOR: They have had some minimal
13 efficacy. I think Amantadine was the first one approved
14 for influenza, and at that time there was nothing else on
15 the market. It had some minimal efficacy in not-that-
16 impressive studies, so it was approved based on the
17 minimal efficacy.

18 Rimantadine, on the other hand, was approved for
19 prophylaxis only because the treatment study wasn't
20 impressive.

21 DR. LASKY: Because one of the issues when we
22 talk tomorrow again about it is the idea of clusters of

1 drugs, and this is kind of coming up as a cluster of
2 drugs. The CDC actually named six drugs, and some of them
3 were on-patent and we couldn't respond to them, and some
4 of them have been mentioned here.

5 If the efficacy isn't demonstrated so CDC is
6 asking for a study to evaluate efficacy, what we have to
7 judge is, is this an important question, not whether we
8 think the answer is one or the other. Just to remind
9 people, is it an important question to study, rather than,
10 do we think the outcome is a negative finding.

11 DR. BAYLOR: It had minimal efficacy in the
12 studies for approval, and at this point I think, with
13 other agents available, the toxicity outweighs the
14 benefit.

15 DR. WARD: Dr. Wiederman, do you agree?

16 DR. WIEDERMAN: Simply put, Amantadine forget
17 about because of the CNS side effects. There is no use
18 wasting time on that for influenza.

19 Rimantadine, the studies for efficacy were not
20 as good as Amantadine. So it is a maybe, but both of
21 those agents are only active against influenza A. If we
22 are going to do something, and I think we should do

1 something, for the under-one-year-old population, it
2 should be Oseltamivir and whether you can get a study done
3 or not. So I think I'm in agreement with Dr. Baylor.

4 DR. WARD: Wayne is suggesting and you are
5 making the very same suggestion that if you want to write
6 in something about Tamivir, to go ahead and do that.

7 DR. BAYLOR: Is Oseltamivir on-patent or off-
8 patent?

9 PARTICIPANT: On-patent.

10 DR. BAYLOR: Okay. We can't use BPC funds to
11 study on-patent drugs, folks.

12 DR. MATHIS: You actually can. I mean, there is
13 a process for referring studies to the NIH. The question
14 is, would we need to do animal studies, which we can't
15 issue a request for. We can only issue written requests
16 for pediatric studies.

17 So we could ask for human studies of Tamivir or
18 Oseltamivir, but we would first need some animal studies
19 to clarify the animal studies that have already been
20 performed.

21 DR. LASKY: I think that is getting way off the
22 task, but the task today is to come up with a list of off-

1 patent drugs for study under this provision with this pot
2 of money.

3 What happens in many of these discussions is
4 everybody just says there is a more current drug that
5 needs to be studied, but that is not what this day is
6 about. This day is about studying off-patent drugs,
7 whether there is something of value in studying it, and we
8 shouldn't get too far astray, I think, from that.

9 DR. WARD: Let me just clarify. Rimantadine
10 still is only effective against influenza A.

11 Am I wrong? A and B or just A?

12 DR. BAYLOR: No, both drugs are influenza A
13 drugs.

14 DR. OVERTURF: I understand you can't ask for
15 patented drugs here to be studied, but what if we are
16 asking for these drugs off-patent to be used as the
17 comparator against patented drugs? In that sense, we are
18 still studying them.

19 For instance, you could conceive of a trial
20 where you actually looked at one of these drugs with
21 Oseltamivir against placebo. One of the things that will
22 facilitate studies now and one of the reasons that we

1 don't have data on these is because we didn't have a
2 facility with diagnosis, and we do now. It is the same
3 thing that plagues influenza vaccine studies, because we
4 have to use influenza-like illness in large studies and,
5 in that case, because you have to look at it every year
6 because of the different strains. Here at least you can
7 look at influenza A strains year after year.

8 You could make a recommendation, it would seem
9 to me, to include off-patent drugs to be compared against
10 patented drugs.

11 DR. LASKY: Yes. That is one of the issues and
12 one of the solutions that we are going to have to engage
13 in, I would think. The way the written request is
14 written, in my experience, is about an off-patent drug and
15 an indication.

16 Now, in some of them FDA has specified it has to
17 be placebo-controlled or active-controlled. I think more
18 of these you are going to want active-controlled, and we
19 can suggest an on-patent drug as a control comparator.

20 DR. OVERTURF: It is the same thing for peer
21 review, the case for things like Acyclovir or Famcyclovir
22 or Valcyclovir, where you have newer generation drugs or

1 essentially pro-drugs for another compound. There would
2 still be some virtue. You might find that the cheaper,
3 older drug actually is equivalent to the more expensive
4 drug.

5 DR. LASKY: I think it is good that you have
6 brought this up because it is not enough to say we should
7 study this. We have to think through, how do you really
8 go into today's environment and ignore current drugs. You
9 can't do studies on 30-year-old drugs, when that is
10 actually what we have to do.

11 DR. PURSLEY: Oseltamivir isn't approved for
12 kids 12 and under. Is that because it hasn't been studies
13 or because it isn't effective?

14 DR. OVERTURF: There was a comment here that it
15 has been studied.

16 DR. BAYLOR: It is one and up.

17 DR. PURSLEY: For prophylaxis?

18 DR. BAYLOR: Oh, for prophylaxis.

19 DR. PURSLEY: I'm sorry. I wasn't clear.

20 DR. BAYLOR: Yes. I'm not positive; I think it
21 has been studied. It has not been turned down, so I'm not
22 sure about that. I know there wasn't a cut-off because

1 there was a problem, so I thought it was approved.

2 DR. WARD: So what I think I'm hearing is
3 another hybrid essentially and a recommendation that
4 studies of a placebo and an on-patent but active
5 comparator be considered. I think that is a fascinating
6 design that has feet in both the on-patent and off-patent
7 worlds.

8 So if you favor that, you can write that in in
9 the margin of the ballot, and we will let Tami figure out
10 how these are going to be tabulated and paid for.

11 [Laughter.]

12 DR. LASKY: For the record.

13 DR. WARD: So Amantadine, Rimantadine. We are
14 down to Methadone.

15 Go ahead.

16 DR. LASKY: I wasn't going to ignore them, but I
17 think also these comments are going to be in the
18 transcript, which is really where they are going to have
19 their greatest benefit. We will tabulate the scoring. It
20 is hard to tabulate comments, but the comments having been
21 part of the transcript will be used in developing written
22 requests and RFCs. So all these ideas are going to be

1 drawn upon.

2 DR. LAWLESS: I have a question for the FDA
3 people. This year, with the purported shortage of flu
4 vaccine, are you guys going to be tracking the use of
5 these drugs this winter in particular before we even start
6 studying them to see whether the utilization of these
7 drugs is increased and whether, again, other side effects
8 are noted or not? It almost seems like it is a forced
9 study going on indirectly.

10 DR. BAYLOR: In influenza, we have a mini team,
11 which I am not on, for influenza preparedness, and they
12 have been keeping track of drug supplies of the drugs and
13 they know how much is out there. We certainly can get
14 records of prescriptions by month, and since Amantadine is
15 used so much in neuro, you wouldn't expect a spike, but
16 you could follow for the flu months when we know flu is in
17 the areas of the U.S. what the prescription rate did, if
18 it jumped or not.

19 DR. LAWLESS: Because if it is done that way, by
20 the time you get the recommendation you may see some early
21 trends of the use of that and other side effects which may
22 change some voting later on.

1 DR. BAYLOR: We certainly can track that this
2 flu season.

3 DR. WARD: Interesting comments.

4 Alan, do you want to talk about Methadone for
5 opiate-addicted neonates?

6 DR. STILES: Sure.

7 **Review of Methadone**

8 **Dr. Alan D. Stiles**

9 DR. STILES: This probably wins the prize for
10 the longest label. It is 19 pages long, and there is not
11 a lot in there. In fact, there is a line or two that
12 basically say it can be used and there is no pediatric
13 information. So I will summarize the label right there.

14 I think there are several issues to be
15 considered here. One is that there is a wide population
16 of variability with this. We have the fetal group. Those
17 would be the maternal Methadone treatments that lead to
18 neonatal addiction. We are evolving a different group now
19 where we have opiate use in neonates that then need to be
20 withdrawn from opiates. Then we have the use of Methadone
21 now in some of the older children as an analgesic. So we
22 actually end up with three different groups of folks who

1 deal with this.

2 We also have the cultural issues that move from
3 unit to unit, and the usual problem we have in neonatal
4 studies that the last line is this needs a well-controlled
5 study to take a look at the question. That is true across
6 the board with this sort of thing. Everyone has their
7 favorite and every unit does it a little different way.

8 There are no studies looking at pharmacokinetics
9 that I could find or that we received looking at this
10 particular drug in neonates, so I think that is just an
11 unknown. Like all opiates, it will depend on when you
12 happen to go after this how much it takes to get it
13 through.

14 One big question is, how do you transition to
15 Methadone from whatever you happen to be on. If you are
16 Morphine or you are on Fentanyl [ph] or on some other
17 medication, how do you transfer someone over to Methadone.

18 There are risks with that with over-sedation and even
19 death associated with transitions in these drugs.

20 To try to deal with this study, you have to
21 figure out how you are going to measure the effect,
22 because that is almost as variable as the number of

1 studies and the number of units are, because everyone does
2 this a little different way and everyone is certain they
3 are right.

4 Then finally, there are some questions raised in
5 the label and other places about increased incidence of
6 Sudden Infant Death Syndrome with patients who have been
7 exposed to Methadone, and then certainly death would be
8 the worst outcome you would expect just from using this
9 medication.

10 DR. WARD: Steve.

11 **Secondary Review of Methadone**

12 **Dr. Stephen T. Lawless**

13 DR. LAWLESS: Actually, ditto to everything Alan
14 just said. Actually, I think the usage is not just in the
15 neonatal ICU. The pediatric ICU is the second place for
16 iatrogenic withdrawal. How to get kids off ventilators is
17 growing as an issue, so it is not just the neonatal
18 population. I would actually assess the younger kids
19 there, also.

20 The other thing, in terms of the impact of
21 prolonged hospitalization of kids who go cold turkey, let
22 them go versus put them on methadone for a couple of weeks

1 while they are in the hospital. There is a cost issue in
2 utilization, and no one knows also the long-term impact on
3 neurologic status of these kids. The brain is developing,
4 fat solubility; what is actually getting in there long-
5 term. So I think there are lots of long-term issues, and
6 short-term, with this drug.

7 DR. WARD: Now we are back to Clonidine.

8 [Laughter.]

9 DR. WARD: Dr. McCune, are you going to discuss
10 this? Who is going to discuss this from the FDA?

11 DR. MATHIS: I actually think that I'm going to
12 cover it, because Dr. McCune had a meeting to go to.

13 **FDA Review of Methadone**

14 **Dr. Lisa L. Mathis (for Dr. Susan McCune)**

15 DR. MATHIS: I think that one of the concerns
16 that Dr. McCune had was that the neonatal intensive care
17 units are actually using another drug preferable to
18 Methadone now for neonatal withdrawal. There are also
19 safety concerns with this drug.

20 I think I have given what has already been said.

21 We didn't have too much to add, other than there were
22 large safety concerns and there may be other drugs that

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1 are better for this indication.

2 **Open Discussion**

3 DR. STILES: Not to steal Dr. Pursley's thunder
4 about sedation and Morphine, the way all of the
5 information that was on the CD about this came out is
6 actually maternal addiction leading to neonatal problems,
7 and we really have this drug in use differently than that
8 now. So we need to think about it again if we are going
9 to continue to use it, as opposed to just the situation
10 where you have the maternal addiction to Methadone and a
11 baby we are trying to get off of it.

12 DR. LASKY: I did the literature search for it,
13 and I found it very, very hard to find articles about the
14 infant. That says to me that it hasn't been studied.
15 When I see that something hasn't been studied, I interpret
16 it as, well, it needs to be studied. I don't think we had
17 the use data. It would be an inpatient issue. So there
18 may be more things we need to learn, but it is not there
19 in the literature, that's for sure.

20 DR. WARD: I would agree 100 percent. I work
21 with a fellow who is actually studying it in the PICU,
22 Ralph Lugo, but in the neonate, I am hard-pressed to find

1 any kind of a guidance for dose, even in a therapeutic
2 concentration range.

3 What you said, Alan, I couldn't agree more.
4 Some of the kids become so sedated, and if they are not
5 adequately monitored and resuscitated from that, they get
6 into big trouble.

7 How are we doing for time? 2:15.

8 PARTICIPANT: Did we have a score on that?

9 DR. WARD: I'm sorry?

10 PARTICIPANT: Did we have a score?

11 DR. STILES: Do we have a?

12 PARTICIPANT: A score.

13 DR. STILES: A score. At least when I scored
14 it, I think I came out with a five, which didn't reflect
15 anything about what I think about it.

16 DR. LASKY: Nobody's score reflected what they
17 thought about it. It was just an experiment.

18 DR. WARD: Tami and I were talking about this.
19 The scoring system is very difficult. I have wrangled
20 with this issue, and there are two ways to score it, I
21 think. You can score it based on exactly the tabulation
22 as indicated, or I think you can even score it and say,

1 look, from zero to 10, do I think this is a two or a
2 three, or I think this is an eight or a nine and really
3 needs study.

4 DR. LASKY: This is part of developing the
5 process. The science of scoring things and scaling things
6 is a whole separate science. You are our first pool on
7 this scoring instrument, so you are unconsenting subjects
8 in a non-controlled trial of a scoring tool.

9 I think one of the things about a scoring tool
10 is that it doesn't necessarily pick up the same thought
11 process that one has when one asks how important do you
12 think something is. This is a different kind of question,
13 which is why it seems that it doesn't seem to fit with
14 people's sense of how important it is, but it does pick
15 important criteria.

16 So for me, who likes to study this type of
17 thing, it is an interesting kind of process to observe,
18 but I think an important piece of information as well,
19 even if you don't agree with your own assessment.

20 [Laughter.]

21 DR. WARD: We have another comment.

22 MS. KAHN: Yes. With regard to Methadone in the

1 peripartum population and the problem of neonatal
2 withdrawal syndrome, there are, as far as I know, only
3 four very small-scale studies of the amount of Methadone
4 which passes into the breast milk in lactating women and
5 how much Methadone has been measured is very small an
6 amount, highly variable, and based on a paucity of
7 information.

8 Nevertheless, the old obstetrical recommendation
9 of avoiding lactation in women who are using Methadone
10 after they give birth has recently been reversed just
11 based on a fair amount, some of it formal, but mostly
12 informal safety experience and the observation, again
13 mainly a clinical rather than a study observation, that
14 the incidence of neonatal withdrawal syndrome is lowered
15 by breastfeeding early in women who are taking Methadone
16 and have just given birth.

17 On the other hand, because there is a lot of
18 variability, that has really been an observation of what
19 appears to be a safe practice rather than actually being
20 recommended that there is an actual reduction in the
21 incidence of neonatal withdrawal.

22 I think that that is a very, very difficult

1 clinical question that needs to be answered and that is
2 not being answered right now by the investigators who are
3 studying women who are in the peripartum period. I would
4 like to suggest that with the recent advent of
5 Buprenorphine, it is now possible to look at a study where
6 we can look at both Methadone and Buprenorphine in this
7 patient population and the implications that it has for
8 breastfeeding and for neonatal outcomes.

9 DR. WARD: Would you clarify what you mean by
10 studying the Buprenorphine as a comparator? You would
11 give that to the mother in place of Methadone?

12 MS. KAHN: Yes, that's right, that's right.

13 DR. WARD: I think the last Committee on Drugs'
14 statement about breast milk drug excretion said that
15 Methadone in therapeutic doses did not pass enough into
16 the breast milk to be a contraindication to breastfeeding.

17 MS. KAHN: Right. It is not a contraindication.
18 It appears not to be a contraindication of breastfeeding,
19 but there isn't a lot of certainty about how much
20 Methadone there is actually passed to the neonate, and
21 that may actually be variable depending on the
22 relationship between the time of lactation, the time of

1 taking Methadone, and the actual period of early milk
2 versus late milk during the lactating period.

3 DR. WARD: It is a very long half-life, so I
4 actually don't think that the variation in maternal
5 concentration will be significant during one or two, or
6 three even, breastfeeding cycles, but the whole area of
7 breast milk drug excretion is dramatically understudied.

8 Wayne.

9 DR. SNODGRASS: Yes. I think there is newer
10 data that the Buprenorphine-Oxone combination is better
11 than Methadone in terms of preventing heroin addicts
12 getting a euphoria. Methadone is long-acting, so that
13 that is the issue here. If during pregnancy it is given,
14 it is long-acting, and withdrawal during pregnancy can
15 lead to fetal death. So the issue then post-birth is how
16 do you deal with that withdrawal.

17 By contrast, with Morphine as an example, we
18 have dealt with some very high-dose, one-gram-per-day type
19 doses in adults of Morphine by IV, and the withdrawal
20 there is 10 days, 10 percent a day, and you don't have
21 what you have with Methadone because it is prolonged. So
22 it is a different phenomenon with Methadone.

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1 DR. WARD: I don't know what to make of that
2 infant death after perinatal addiction with Methadone. It
3 was, as I recall, 23 days or something after birth,
4 whether it was SIDS or whether it was Methadone-related.

5 This is a commonly used drug in the NICU or in
6 the PICU, and certainly, everything that is used in the
7 PICU gets to the NICU sooner or later.

8 People's wishes. Do you want to break now for a
9 break, or shall we just head on down the list? Let's go,
10 okay.

11 Let's do Bupropion for depression and smoking
12 cessation.

13 Dr. Zito?

14 DR. LASKY: I just want to add that these are
15 two on-patent drugs and they come to NIH through a
16 different process. These are drugs for which FDA has
17 already written written requests, and copies of the
18 written requests have been circulated on the tables. The
19 written requests have gone out to industry. Industry has
20 declined the opportunity to do the studies. It gets
21 passed to the Foundation for NIH, which then refers the
22 drugs to us. So they are not competing with the off-

1 patent drugs for the same pot of money, but we are asked
2 to review them.

3 **Review 2: On-Patent Drugs**

4 **Review of Bupropion**

5 **Dr. Julie Zito**

6 [PowerPoint presentation.]

7 DR. ZITO: We can skip down to the story on
8 Bupropion, and I will bring back some Medicaid-insured
9 child utilization data to help you frame the issue of how
10 much exposure kids have to Bupropion.

11 If you look at the first bullet, you see that
12 about 3 percent of the kids zero to 17 years of age
13 received one or more prescriptions for an antidepressant
14 in the year 2000 in this Medicaid state population. So we
15 are growing, particularly when you add, of course, the
16 older age group, 15 and up.

17 The bulk of that is represented by SSRIs, which
18 should be no surprise, and now, since the news and the
19 chaotic events that have been second place and the black
20 box warning, it has reframed the way I'm thinking about
21 presenting this drug to you today.

22 TCAs have been demonstrated in younger age

1 children to be not effective to treat depression. Younger
2 age kids are 12 and under, typically. So there would be
3 no falling back to TCAs as an alternative to SSRIs.

4 Now, the group called "Other Antidepressants" is
5 where Bupropion is hidden, and so when you separate out
6 Bupropion from the other members of that group, you see
7 that the bulk of utilization for the other antidepressants
8 is in fact Bupropion. So there was substantial use of
9 this drug in these data.

10 Now, we split it out by age group. Of course,
11 the 12 to 17 are the largest users of Bupropion, but five
12 to 11 is pretty substantial. That is where we get into
13 concerns about differential effects, because it is pretty
14 easy to demonstrate that depression, if we are talking
15 about depression -- and already I have skipped over a
16 whole bunch of issues about the fact that there is no
17 diagnostic data there, so I shouldn't be making those big
18 assumptions. It could be ADHD, it could be comorbid
19 depression with ADHD. But the five to 11s are pretty
20 substantial.

21 Now, if we look by race and ethnicity, again,
22 the predominance there is pretty substantial. So there is

1 a good race/ethnicity basis for examining data by
2 race/ethnicity. Of course, in gender again, it is the bad
3 boys who are seen to be pretty substantial in use.

4 So that's it for that.

5 So in deference to my husband, who is a chemist,
6 I actually got the structure, and you can see that in
7 contrast to the promotional material, this drug is
8 different from any other drug in the category. It has
9 very much comparable activity, although slight differences
10 in terms of dopaminergic reset and reuptake blocking.

11 Bupropion has, I put up there, indications for
12 major depression, ADHD, and comorbid depression. The
13 smoking cessation, I guess, we could add in since you did
14 suggest it.

15 There will be drug interactions that we might
16 worry about if it were to be used in combination with
17 drugs that typically are competitive inhibitors of
18 metabolism.

19 We have a long half-life, so a long half-life
20 after chronic use means about essentially a 24-hour half-
21 life, elimination half-life. It does pass into breast
22 milk, so we have to think about those 16-year-old mothers

1 and young women who are out there that might be on the
2 drug.

3 The good news is no cardiac conduction relays
4 [ph] have been demonstrated, which has been a big problem
5 we see with TCAs.

6 By 1985, Bupropion had been evaluated in over
7 3,000 adults, and there is substantial experience with
8 this drug in adults. I think the initial enthusiasm for
9 the drug was very much dampened by the fact that it has a
10 substantially higher risk of seizures, and we will talk
11 about that more in a minute.

12 Pediatric studies, according to the label, have
13 occurred in a very small number of six- to 16-year-olds,
14 and so there is insufficient data.

15 So in '85 for depression for Wellbutrin tablets.
16 Then in '96, the SS and the SR, and in 2003, the XL, and
17 since '97, smoking cessation.

18 Contraindications. People with anorexia,
19 bulimia, or at higher risk for seizure would all be people
20 that should not use this drug except in very limited
21 circumstances.

22 Drug interactions I'm going to skip over, but

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1 essentially the more you combine seizure-lulling potential
2 drugs, the higher the risk would be. We have learned a
3 lot about how to reduce the risk of seizure with this
4 drug. So if we keep the dose below 400 milligrams a day,
5 the incidence drops down to comparability to a TCA.
6 Unfortunately, use of combinations now is becoming so
7 prevalent that we really have to worry about the way we
8 use it.

9 A lot of the data that we are looking at would
10 suggest that comorbid depression in kids who have ADHD and
11 are being treated with stimulants explains combination use
12 with some antidepressants, typically with an SSRI, and
13 now, what are we going to do about that.

14 The warning is around seizures, which I
15 mentioned, and the increased risk when you add in other
16 drugs that control the seizure.

17 I noticed in looking at the handouts that you
18 gave us, the package inserts, that the company has put in
19 a new statement beginning in April -- it is dated April
20 '04 -- which states the following, and it is all about the
21 suicidality issue. I have listed it here. You can read
22 it for yourselves.

1 It is a very convoluted problem. I don't know
2 how we are going to get around it because it seems to
3 suggest that treatment, and in some instances people are
4 saying effective treatments for depression and for
5 suicide, would increase your risk because you are getting
6 better and you are getting well enough to harm yourself.

7 I don't know how to explain this stuff to the
8 public and really get them to believe that we know what we
9 are talking about, but there is a strong tradition within
10 psychiatry to say people have experienced it and people
11 have gotten well enough to kill themselves, so I don't
12 dismiss it. I just find it incredibly difficult for us to
13 deal with.

14 Precautions are all about how much in a single
15 dose because of the risk of seizure.

16 Now, the agitation anxiety is one of those
17 problems that the SSRIs have. It would be really nice to
18 know if we could do a better job in seeing lower rates of
19 emotionability or agitation or anxiety, the kinds of
20 things that they are worried about with the SSRIs.

21 Skin rash shows up over and over in the studies,
22 and sometimes hypertension occurs, and that seemed to me

1 to be more in the adult literature.

2 So there are a bunch of symptoms here that are
3 called neuropsych symptoms that fall under the category of
4 behavioral toxicity. It will be hard to tease apart
5 whether this is the underlying illness or whether it is a
6 symptom that has broken loose, so if we study this drug, a
7 good bit of effort ought to go into being able to look at
8 those things.

9 I didn't really find anything about kinetics in
10 the information here, except that they do mention that the
11 drug has been studied in about 104 children.

12 So my recommendation on efficacy is based on the
13 fact that this is not an SSRI, not an nSSRI. It could
14 become more important as an alternative drug for the
15 treatment of either major depression or comorbid
16 depression.

17 It represented about 22 percent -- [off mic].
18 So it is not insignificant in its use. The racial stuff
19 is interesting.

20 A brief review of the drug by Connors and
21 others, and a number of studies were done to evaluate it
22 for the treatment of ADHD. I don't know if it is a world

1 leader or not. Some of the studies imply improvement.
2 There is a subgroup set of kids who do not respond well to
3 stimulants, and of course, Strattera is available now and
4 that is in the same category and class of drugs. So there
5 is probably something to it as an ADHD treatment for the
6 child, and there is at least one study on ADHD.

7 Again, those neuropsych symptoms. Side effects:
8 anxiety, agitation, hostility. All of them really need
9 to be considered in studies that we would use to evaluate
10 children.

11 Now, the next one here is telling you to go to
12 the FDA website. There you can find a vast amount of
13 information that fed into the FDA's reporting to the
14 public on how they got to where they are on the SSRI
15 issue.

16 There are actually two studies mentioning
17 Bupropion. Neither one of them seems to be real or at
18 least to appear in the report. One had no evaluable risk
19 information. There was no suicidality reported. Then in
20 the other one, they said the study wasn't available.

21 Finally, a very recent 2001 paper suggested that
22 the sustained release form for adolescent depression

1 comorbid with ADHD was an open study. So the science of
2 this study really leaves a lot to be desired, but they
3 have come out saying they find the effects they are
4 looking for. There is an effect there.

5 The hypothesis that I would pose to be evaluated
6 is an antidepressant, in particular focusing on younger
7 age children versus older age children, because there is a
8 good deal of data to suggest that depression does not
9 respond well to meds. So that would be really helpful if
10 we could do that.

11 And then, paying some attention to tolerability
12 and acceptability. So getting at efficacy, not very
13 short-term but over the course of a year, and of course,
14 really measuring epileptic effects, would be essential to
15 satisfy ourselves that we know how to use this med better
16 now than we did when it first was marketed. Is it a
17 reasonable alternative to the SSRIs, is one question that
18 could be addressed.

19 Finally, thinking about a large cohort study,
20 because seizures are not that common and suicidality is
21 extremely difficult to study. So we have some practice
22 networks, volunteer networks, and then we have very large,

1 organized treatment settings, like HMOs, that seem to be
2 reasonable settings in which we could collect the type of
3 information that would be ultimately most helpful.

4 DR. WARD: Dr. Woo.

5 MS. WOO: I'm not a doctor yet. I haven't
6 finished my Ph.D. quite yet. I'm almost done.

7 **Secondary Review of Bupropion**

8 **Ms. Teri Moser Woo**

9 MS. WOO: Anyway, I just want to note that the
10 labeling says that "It should be noted that Wellbutrin is
11 not approved for use in treating any indications in the
12 pediatric population." That is what their label says.

13 Now, those of us that are in pediatric primary
14 care know that this drug is being used, and it is kind of
15 concerning when you get into the literature what it is
16 being used for and the fact that there is very little data
17 to support its use.

18 There are very few studies about its use in
19 depression, and the studies are small sample sizes without
20 adequate power to really prove what they are trying to say
21 that they want to use it for. It is being used for ADHD
22 with very little data to support that, and it is being

1 used in younger kids without data to support that.

2 It is a real concern, especially with the
3 seizures. The seizures are dose-related, and there is no
4 real clear dosing guidelines for younger kids supported by
5 good RCT studies.

6 There is also concern that they are taking a
7 stimulant such as Ritalin; does that decrease the seizure
8 threshold, taking these drugs together. That is a concern
9 for me.

10 There is no dosing really in the literature for
11 ADHD, even though it is being proposed in some studies for
12 use. Once again, those studies were small.

13 I think the main things that we need to look at
14 is the PK/PD in younger kids. We are using it in kids
15 that are six- to 12-year-olds, and we are not really sure
16 what is going on with Asitacome B450 2B6 [ph] at that age
17 and how this drug is being metabolized in that age group.

18 Luvox, was that relabeled in that age group? The dosing
19 was different in that specific age group based on the
20 pharmacokinetic studies.

21 My recommendation, I gave it a seven-plus. I
22 think this does need to be studied. I think the group

1 really needs to push this, and it is unfortunate that they
2 have already addressed it with the drug company and they
3 have kind of not wanted to relabel it for pediatric use,
4 because it is really concerning to me that we are using it
5 in pediatrics with so little good, solid data for it.

6 That's it.

7 DR. WARD: Do we have representation from the
8 FDA?

9 DR. SACHS: That's me.

10 **FDA Review of Bupropion**

11 **Dr. Hari Cheryl Sachs**

12 DR. SACHS: I'm glad you clarified that. It is
13 actually approved in adults for both major depression and
14 smoking cessation, but not in kids.

15 While there certainly are some alternatives for
16 depression in children, only one is approved. There are
17 some alternatives for smoking cessation. Again, none are
18 approved in kids. Most of them are over-the-counter. Of
19 course, the big concern in studying this would be the
20 seizures.

21 As far as depression goes, I think people are
22 pretty much in agreement we need some good drugs in

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1 depression. Whether this is the drug is not necessarily
2 clear. As far as smoking cessation is concerned, there
3 are 3.8 million kids under 18 that smoke. Again, whether
4 they are addicted is another story. This drug, it would
5 seem to me, would need to be used in kids who are
6 addicted, especially if there is some risk of seizures.

7 Obviously, the FDA Review Division, we did issue
8 a written request for both these indications, and so from
9 the FDA point of view, this would be a drug that we would
10 be very much interested in studying.

11 **Open Discussion**

12 DR. WARD: Did the Review Division discuss ADHD?

13 DR. SACHS: ADHD was not discussed. As far as I
14 know, in the written request, they did indicate that if we
15 had to choose between these two indications they would
16 rank depression over smoking cessation.

17 DR. LASKY: I don't think everyone is aware. As
18 I mentioned, these are on-patent drugs, so FDA has already
19 written a written request. The written requests were
20 handed out at lunchtime. Our reviewers, when they were
21 asked to review the drug, were asked about Bupropion and
22 depression, and we didn't ask about the smoking cessation

1 indication.

2 I think at NIH we would prefer that the two
3 indications be separated, and maybe they should be
4 separated on the scoring sheet.

5 We actually, at NIH, didn't really understand
6 that aspect of the written request, so if you can
7 elaborate on it a little bit, and if the group could react
8 to that specific indication as well.

9 The indication of depression is a little more
10 clear and comprehensible, but the idea of
11 pharmacologically treating children for smoking cessation
12 as young as 10, as is suggested in here, is a little
13 harder to understand.

14 DR. MATHIS: Just as far as addressing what
15 indications are in the written request, as we are
16 formulating written requests for on-patent drugs, we are
17 forced with making the choice between on-label and off-
18 label indications. We cannot combine the two in a written
19 request. That is a legal decision that has been made. So
20 that may be why ADHD does not appear on this written
21 request. These are the two on-label indications.

22 The other thing is, we don't generally issue

1 written requests with just one indication on it when there
2 are two labeled indications that we are interested in,
3 because that would give industry the opportunity to choose
4 which study they are going to do, and frequently, it ends
5 up not serving the pediatric population because they tend
6 to go where the easiest study is or where the smallest
7 study could be rather than studying that population where
8 there is the greatest public health benefit.

9 So that is why you see these two indications
10 showing up on this written request and no ADHD.

11 As this moves into the arena of NIH, how they
12 handle it from a contract standpoint can be very different
13 than how we can handle it as a written request that is
14 going out for an on-patent drug.

15 DR. WARD: Let me just push that a little bit,
16 then. If the NIH requested ADHD in addition to depression
17 and smoking cessation and data were obtained with respect
18 to ADHD, yet it has never been labeled for ADHD, how would
19 the division or how would the FDA be able to handle that?

20 DR. MATHIS: Well, any study that is done, if
21 people plan for it to be incorporated in the labeling,
22 would have to be submitted as a labeling supplement or an

1 efficacy supplement. This would have to be an efficacy
2 supplement because it would be a whole new indication.

3 That would be very difficult to do without the
4 sponsor, unless of course the FDA issued a separate
5 written request for ADHD, which could be something that
6 the division could consider at this point.

7 DR. SACHS: You asked one question about smoking
8 cessation and why, maybe, this drug would be chosen. We
9 talk a little bit about a concern in depression, of
10 course, would be if you have weight loss, that could
11 affect growth of kids. That may be a significant thing.
12 We certainly found that to be true for Veloxitine.

13 If you think about it for smoking cessation,
14 weight loss would be a little attractive, because most
15 people that discontinue smoking are concerned about weight
16 gain.

17 DR. WARD: This looked like it was 2B6
18 metabolized, and I will ask Jeff, do we know whether it
19 has similar ethnic diversity in its polymorphism as far as
20 slow metabolizers as 2D6 does?

21 DR. BLUMER: Well, 2B6 doesn't have the same
22 ethnic differences. There are three isoforms, one of

1 which is a NO isoform. So you would expect there to be
2 slow metabolizers. Of course, this is the barbituric
3 response to the isoform of B450.

4 DR. WARD: Other discussion?

5 Wayne, yes.

6 DR. SNODGRASS: Are there any patients, adults,
7 with depression that don't respond to SSRIs that will
8 respond to Bupropion? Is that a known entity? In other
9 words, where does Bupropion come in on the drug choice
10 list?

11 DR. WARD: I just don't know. You are certainly
12 out of my arena there.

13 DR. MATHIS: I'm not aware of any data.

14 DR. WARD: There is the issue of considering a
15 different mechanism of action.

16 DR. SNODGRASS: Well, I'm also thinking of just
17 risk, benefit, and risk.

18 DR. SACHS: This drug does still have a black
19 box warning, too.

20 DR. WARD: With respect to seizures?

21 DR. SACHS: Well, no, with respect to
22 suicidality, which I just mention, again, because there is

1 a part of me that says if the speculation is there is any
2 increased risk because of the underlying disease, if you
3 are studying a group for smoking cessation and you saw an
4 increased risk of suicidality, that would definitely let
5 us know it is the drug. On the other hand, is it
6 unethical or risky to study a population that doesn't have
7 a risk of suicidality with a drug that might.

8 DR. WARD: But is the black box warning a "me
9 too" because of the SSRIs, or is there direct data?

10 DR. SACHS: It is part of the whole warning.

11 DR. WARD: It is the "me too" thing.

12 DR. SACHS: All the drugs got labeled.

13 MS. WOO: Also, there was a study about using
14 this with kid with comorbidities and they were talking
15 about asthma, but I am also concerned with some of the
16 other comorbidities our adolescents have, like OCD and
17 some of the other drugs we are putting some of these kids
18 on, and we are adding in Wellbutrin.

19 I think we are seeing a lot more drug
20 interaction and psychotropics in adolescents, which used
21 to be an adult problem. I think we really need to look at
22 this drug as well. We need to start looking at

1 comorbidities.

2 DR. WARD: I would just observe that
3 polypharmacy with psychoactives in children seems to be
4 the rule, not the exception.

5 PARTICIPANT: It is scary.

6 DR. WARD: Yes, I would agree with that.
7 "Scary" is the right word.

8 DR. ZITO: There is a not-so-funny joke. You
9 can't be on more meds than your age.

10 [Laughter.]

11 DR. WARD: Let me suggest that we do what Tami
12 recommended, and that is that we handle votes for
13 depression and for smoking cessation independently of each
14 other. If they are the same, obviously they are the same.

15 PARTICIPANT: And ADHD?

16 DR. WARD: I'm unclear what to do with ADHD.
17 The issue is exactly as Dr. Mathis said, and that is that
18 if we want to propose a new indication, it requires a
19 full-bore efficacy trial. I think we would probably be
20 able to rely on previous PK studies, but efficacy, safety,
21 et cetera. Dose ranging, probably.

22 PARTICIPANT: And two. You need two.

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1 DR. MATHIS: We could take information back to
2 the Review Division as well. I mean, if people felt very
3 strongly about that, we would be happy to share that with
4 the Review Division.

5 DR. WARD: So the answer would be, if you feel
6 that it should be studied in ADHD, write that in. Let's
7 go ahead and vote at this point on the two that are before
8 us of depression and smoking cessation.

9 Yes.

10 DR. ZITO: Let me make a complication here and
11 think about a study design in which depression is a
12 comorbidity of ADHD. There is a very substantial pool of
13 kids out there like that. So you could be brought in
14 because you have depressive symptoms, but MDD might not be
15 the only criteria for entry into the evaluation. So like
16 the early suggestion, we might get more bang for the buck.

17 DR. WARD: I think that is probably best carried
18 back through the recorded comments and transcribed
19 comments as a study design issue.

20 DR. ZITO: I also want to make a comment around
21 the smoking cessation. I have two big concerns there.
22 One is that the older you get, the less like pediatrics

1 you are, or the less likely are concerns about pediatrics
2 there. So smoking cessation just isn't as big a problem
3 for me as is defining efficacy and safety in a pre-pubital
4 population. That is one issue.

5 The second is, I was trying to think about how
6 you would engage kids, because here is an example where
7 the behavioral pattern is very peer-driven, it is very
8 age-driven. It has almost nothing to do with pharmacology
9 except I see it as a big deal for really long-term
10 addicted smokers that you use pharmacology to get them
11 through the early stages of coming off cigarettes.

12 I am wondering what scenario we have here in
13 terms of who we want to study for smoking cessation. Not
14 that it isn't an important issue in teenagers, but I just
15 don't know what is new here that would be different and
16 how you would be certain that you would not be just
17 describing or mandating pharmacologic studies in the
18 absence of behavioral intervention.

19 DR. WARD: That is a legitimate question, but I
20 think that is also back to a design issue.

21 DR. SNODGRASS: I'm going to ask, along the same
22 line, how strong is the data that Bupropion is effective

1 in smoking cessation? I thought it was only in
2 conjunction with significant behavioral input, 20 percent
3 or 30 percent without.

4 DR. MATHIS: The current labeling does put it in
5 the context of behavioral therapies as well, and the
6 written request does that, too. I mean, that is a major
7 component of treating smokers.

8 DR. SACHS: Like I said, I was trying to raise
9 the difficulty of identifying a group of smokers and
10 adolescents who are truly addicted. I know one cynical
11 thing that I read in some of the studies was that we might
12 as well wait until they are 18 and then you can really
13 study them as adults.

14 DR. LASKY: They not only have to be addicted,
15 they have to be interested in quitting.

16 [Laughter.]

17 DR. LASKY: And motivated and willing to
18 participate in such a study.

19 I know one of the things we are going to try to
20 do is quantify the underlying conditions that we are
21 trying to address here, and I'm very curious about the
22 number of kids who are truly addicted and motivated to

1 quit at the same time.

2 DR. MATHIS: But I think that we have to be
3 really careful not to underestimate the public health
4 benefit of getting kids to quit smoking, because people
5 who are lifelong smokers have usually picked up the habit
6 before they are 18 years of age. If we can break that
7 cycle, perhaps we can prevent some of the long-term
8 illnesses that come from lifelong smoking.

9 Kids can become addicted to nicotine just like
10 adults can. It is no less addicting in children than it
11 is in adults.

12 DR. WARD: Yes, Bill.

13 DR. RODRIQUEZ: Dr. Zito, your comment about
14 depression and ADHD, how frequent is the depression in the
15 ADHD patients?

16 DR. ZITO: I don't know the answer to the
17 depression. Maybe Dr. Vitiello could answer that. I do
18 know the utilization data, so I know that there is
19 increasing use. So my assumption is that the depressive
20 symptoms are there.

21 DR. VITIELLO: Right now, Bupropion for
22 depression could be like a third-choice drug. It is very

1 difficult because of the issue about the black box and if
2 this would change. But right now, the first choice is an
3 SSRI. The second choice, if the SSRI fails, is another
4 type of SSRI, and then the third choice is probably
5 Bupropion or something in that neighborhood. So right
6 now, it is the third choice, but this may change.

7 DR. RODRIQUEZ: That was my question. If this
8 were to become effective, the indication would be
9 depression in patients with ADHD, right? It would be
10 depression?

11 In other words, if the patients that are studied
12 with depression have depression with ADHD, that would be
13 the indication?

14 DR. VITIELLO: Yes.

15 DR. RODRIQUEZ: Okay. Thank you.

16 PARTICIPANT: I just want to comment that I
17 think there is a study in teenagers that, after two weeks
18 of a pack a day or more, you are addicted. It doesn't
19 take long and it doesn't take much. I don't think there
20 is any comparator to the inhaled prescription nicotine
21 approach.

22 DR. WARD: I personally would not underestimate

1 the health impact of young children starting smoking. You
2 can just walk down the street, and it is pretty young.

3 So we are back to write-in candidates for ADHD
4 and Bupropion for depression, and smoking cessation
5 handled separately in the scoring system, okay?

6 Morphine for sedation. Dr. Pursley?

7 **Review of Morphine**

8 **Dr. DeWayne M. Pursley**

9 DR. PURSLEY: We have had a number of
10 discussions about Morphine over the last few hours. One
11 of the problems that we first encountered was that there
12 was a discordance between the agenda, which was suggesting
13 that the indication was sedation, and the actual letter,
14 which suggests that the indication was analgesia. That is
15 okay, because it reflects what is going on, I think, in
16 some of our intensive care units.

17 Further, it was complicated by the fact that the
18 label was for the oral form, although the 19 studies that
19 were referenced and provided on the CD were for IV,
20 epidural, and sublingual for indications as disparate as
21 spinal surgery and mucositis, and with outcomes that not
22 only included pain but nausea, vomiting, and pruritus.

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1 I think in this situation is probably helpful to
2 at least start with what I am familiar with. I think what
3 is happening in neonatal intensive care units is mirrored
4 in some ways with the rest of pediatric care.

5 It might be helpful just to take a step back and
6 talk a little bit about how pain management has evolved.
7 I think talking to some of the older neonatologists it
8 seems like we have started with an era where there really
9 wasn't a concern about pain management in newborns. There
10 was a presumption that their central and peripheral
11 nervous systems were immature, if not primitive, and that
12 pain wasn't really appreciated by newborns.

13 Thankfully, we got away from that era, but we
14 sort of went the other way, and things really jumped when
15 we discovered IV phetinol [ph], I think.

16 Probably, more recently -- and by more recently,
17 maybe the last five years or so -- we have entered into a
18 period of introspection where we are trying to understand
19 what the right thing is and understanding that there is a
20 difference between using pharmacologic agents for sedation
21 and using pharmacologic agents for analgesia.

22 About four or five years ago, the AAP came out

1 with a statement on pain control in newborns which
2 encouraged the use of validated measures for pain. One of
3 the problems, of course, is that it is difficult to
4 discriminate between pain, stress, and normal variations
5 of behavior, and awake and sleep states in newborns.

6 My kids cry, they scream, and they have variable
7 behavior, but I have found that behavioral and
8 environmental interventions are effective, and I haven't
9 had to resort to pharmacologic agents.

10 So the ADP sort of got us, I think, refocused on
11 pain management in newborns and suggested that
12 environmental and behavioral interventions should be
13 utilized as much as possible and pharmacologics used as a
14 last resort. They also suggested that only pharmacologic
15 agents with proven efficacy and safety be utilized,
16 whatever those might be.

17 There is a consensus statement that came out
18 about three years ago in which they focused, thankfully,
19 on specific interventions, what interventions in the NICU
20 actually require pharmacologics. Their consensus was that
21 it required nothing more than lidocaine, either topical or
22 injected, and sucrose on pacifiers has proven to be a

1 prevalent intervention in neonatal ICUs.

2 In fact, the only indication for opioids
3 mentioned in that statement was for thoracostomy tubes. I
4 think that most neonatologists would agree that that is
5 something that required fairly aggressive pain control.

6 Then, more recently, in fact a year ago, JAMA
7 published a study that was done by a large group of NICUs
8 examining the routine use of narcotic infusions in their
9 units, because in the era in which we assumed that all
10 babies were in pain, many NICUs were actually managing
11 their babies with intermittent Morphine dosing, if not
12 continuous narcotic infusions.

13 They found that there was no measurable
14 analgesic effect with the narcotic-managed babies as
15 opposed to placebo. There didn't appear to be any effects
16 on neurologic outcome, and they expressed a concern about
17 what the long-term use of these medications might result
18 in.

19 Then, six months ago, another group of NICUs, a
20 group called Neopain, published their study, in which they
21 examined differences in outcomes between babies who were
22 managed with continuous infusions and not. They found

1 that not only did the infusions not appear to be helpful,
2 of any benefit, but for those babies who were receiving
3 placebo and received open-label Morphine, there actually
4 appeared to be worse neurologic outcomes in that group.

5 The Committee on Fetus and Newborn has embraced
6 this issue and is looking at this most recent published
7 data. My sense is, and I have plenty of people to ask
8 here, that neonatologists and NICUs are trying to sort of
9 move away from this and trying better to distinguish
10 between appropriate sedation, which might in fact be
11 better managed with appropriate behavioral and
12 environmental controls and analgesia, where analgesia is
13 needed in an aggressive manner, such as with a thoracic
14 tube placement.

15 So that is at least one neonatologist's
16 perception of what is going on with that age group. I
17 would invite other people to educate me as to what might
18 be happening in pediatric ICUs and within the ORs.

19 So I will just stop right there for right now.

20 Secondary Review of Morphine

21 Dr. William E. Berquist

22 DR. BERQUIST: Yes, thank you. I agree there

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1 was a little confusion about what we were trying to do,
2 but the letter was very helpful to clarify that.

3 First of all, the premise is Morphine Sulfate is
4 commonly used for analgesia in the intensive care units.
5 I think with that premise, then you say, well, how best to
6 use it. Actually, when I reviewed all of those different
7 studies, this is a great drug to do PK/PD studies on. You
8 can see that come through. I mean, our anesthesiologists
9 and pain people have a great forum to do those kinds of
10 studies.

11 Most of these studies are, again, what are we
12 doing; what is convenient; how much you study it. So they
13 pick different groups, and then they look at the different
14 doses. The problem is, they combine it with different
15 combinations, but at least they are able to get some data
16 as to dosing.

17 So I would gather that the question is, even
18 though they have done a number of these studies, we are
19 still not absolutely sure about what is the sort of proper
20 dose to use and to recommend for Morphine, again, as a
21 single agent.

22 As such, I think there is probably room to

1 pursue that, because it is a very definable kind of
2 question. So I think once you look at the letter, then
3 you could say, well then, now maybe I understand what you
4 are after. We were given an oral preparation, and that
5 got me confused. Then I looked at the literature, as did
6 DeWayne, and I think that really helped me to understand.

7 DR. WARD: The written request is actually
8 specifically stated for analgesia, even though the yellow
9 ballot form says "for sedation."

10 Dr. Sachs, are you going to comment from the
11 FDA? Or, Dr. Mathis?

12 DR. MATHIS: Dr. Beckman was actually scheduled
13 to cover, but had to go to another meeting.

14 **FDA Review of Morphine**

15 **Dr. Lisa L. Mathis (for Dr. Hari Cheryl Sachs)**

16 DR. MATHIS: Basically, what she had put
17 together was very much in the vein of what we have just
18 heard, that there is some data out there now from the
19 Neopain study and from the previous study that questions
20 the efficacy, we don't have good PK/PD or dosing, and
21 based on these three things and the large amount of use,
22 it would be a very good drug to study.

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Open Discussion

1
2 DR. WARD: We were in the middle of planning two
3 studies of Morphine in neonates when Sonny's paper came
4 out, or when it was about to come out, in the spring. You
5 have to read it very carefully because the kids who had
6 the neurologic injury were generally those, exactly as Dr.
7 Pursley said, who were receiving it in the placebo group
8 outside of the infusion but also had hypotension.

9 So I think the issue about -- I have a slide
10 about it -- it is the dose, it is the dose, it is the
11 dose. This, I think, is a classic example where we
12 probably don't have the dose right. We may not even have
13 the right indication, but it is used widely.

14 Jeff and Steve, I think it is growing in use in
15 PICUs as well, but I don't know that. No? Fentanyl [ph]
16 is still the standard?

17 DR. LAWLESS: Jim, you know a lot more than I do
18 about it, but I mean, the use of Morphine, actually, is
19 probably decreasing. Fentanyl has taken over in the
20 operating room. I can't remember an OR sheet that I have
21 seen for years that has actually had the word "Morphine"
22 on it. They are way beyond all that stuff.

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1 DR. BLUMER: When we surveyed groups in
2 preparation for the Lorazepam trial, it turned out that it
3 is about 50/50, and it varies. The indication is pretty
4 interesting because when you talk to people about how they
5 use it, I mean, to some extent we are treating ourselves.

6 I mean, it is not clear that we are treating patients.

7 We believe that patients have pain, and it
8 depends on what your current religion is. So those are
9 the patients that get opiates. It is a real problem.

10 DR. WARD: Dr. Higgins.

11 DR. HIGGINS: One of the other issues that
12 underlies the charge of this committee but goes along with
13 what Dr. Blumer is saying is JCAHO has issued some
14 guidelines for pain being either the fifth or sixth vital
15 sign, depending if you count oximetry as a vital sign. So
16 that is one of the overriding issues that is facing
17 intensivists and folks that work in the OR that probably
18 should be sort of kept on the radar screen with this drug.

19 DR. WARD: Let me just echo, also, this issue
20 about validative scoring tools. SciAnon [ph] has a second
21 edition of a book called "Neonatal Pain," in which Bonnie
22 Stevens states probably five times there is no gold

1 standard for determining when a neonate is in pain. We
2 still struggle with that. We do the best we can. We try
3 to follow JCAHO's requirements to monitor it, and it
4 enters into how you design a study, certainly, for testing
5 these drugs.

6 DR. LAWLESS: Again, this is a part of the
7 JCAHO, and even their latest thing about using disk
8 monitors and everything else, I mean, there is a nice
9 element of consumerism there. It sounds really nice, but
10 in terms of practicality, it is sending a false sense that
11 this is actually very easy to control.

12 DR. WARD: And to measure.

13 DR. LASKY: Just to help clarify this, the
14 written request asks for kids from one month up to 16
15 years. Are there any comments from the reviewers on the
16 age distribution? Is this too wide; is this appropriate?

17 DR. PURSLEY: I would think that the issues
18 would be different for the one-month-old than the 16-year-
19 old.

20 [Laughter.]

21 DR. PURSLEY: Conducting a study, I think, would
22 be very difficult for the reasons that have been expressed

1 here and in children that can't tell you that they are in
2 pain.

3 DR. MATHIS: Just to clarify, that is the
4 pediatric patient age group. However, there is also a
5 neonatal patient age group. If you look right above that
6 in the written request, there is preterm infants and term
7 infants to less than one month of age. So all age groups
8 have actually been covered in the written request.

9 DR. PURSLEY: I think I understand what started
10 this, but my impression is that what is happening in the
11 section and what is happening in our NICUs right now in
12 terms of their focus on this as illustrated by our chair's
13 interest, is what should be happening, that sense of self-
14 examination.

15 I'm wondering if, after some time, there would
16 even be sufficient equipoise to do a randomized control
17 study of this.

18 DR. WARD: Well, the Neopain study, as well as
19 the previous one, No Pain, were randomized and controlled,
20 but there was the escape mechanism, if there was pain
21 detected, the child got treated outside the study. That
22 is really the issue, as Jeff points out. Are they in

1 pain, or what are we treating.

2 DR. LAWLESS: Unfortunately, or fortunately, I
3 come from a hospital system where we have a cardiac ICU
4 person who used to profess that he does not give or did
5 not give any analgesia to his post-op patients.

6 Now, the trouble is, his mortality rates were
7 far less than everybody else's, his length of stay, all
8 quality measures were tremendous. So a hard pill to
9 swallow.

10 DR. BERQUIST: This actually is an area of
11 conflict. In liver transplant, we run into the same
12 issues. The same thing with GI patients. You start
13 pushing opioids and then you run into all the side effects
14 and problems. It just reemphasizes the importance of
15 studying and looking into pain management.

16 I think the premise, though, that Morphine is
17 the most common is perhaps a question. Is that the drug
18 we should choose or not. I think the idea is very good,
19 though, that these things really need to be looked at,
20 especially with the giant commission pushing.

21 DR. WARD: Jeff.

22 DR. BLUMER: Two other comments. One, if you go

1 back to the issue with sedation, then it becomes an
2 important issue because, given the various receptors that
3 exist for opioids, it is not clear that all of them or
4 that the new receptor, for example, is the receptor for
5 sedation. So when you start thinking about the way that
6 we use these drugs in both intensive care units as an
7 adjunct to sedation in many cases, they are generally not
8 used alone.

9 That's fine, if you think about using them with
10 a benzodiazepine, but if you are using them alone, then
11 there may be -- I shouldn't say there is -- there may be a
12 difference between Fentanyl and Morphine.

13 The second thing, and one of the things that
14 confounded the Neopain study certainly -- one of the two -
15 - where you begin to look at long-term outcomes. Despite
16 the group that you are randomized to, if you have that
17 escape clause and if those patients get non-protocol
18 opioid, unless you drop out all the patients who get put
19 on the placebo arm, for example, you will never be able to
20 look at these long-term outcomes. It seems to be one of
21 the driving forces behind a lot of these issues.

22 DR. WARD: I have thought at length about how do

1 you analyze such a study. I think at some point you have
2 to get out of the intention to treat mode and look at
3 total dose and response and outcome.

4 DR. SNODGRASS: There is no PCA for neonates
5 because they can't give it to you.

6 DR. WARD: We are the PCA.

7 DR. SNODGRASS: Right. So they can't be telling
8 you. So that is one issue that is fundamentally different
9 than the older age group studies.

10 The other is that 30 percent of patients in any
11 placebo group in these adult pain trials get some pain
12 relief, and then if you measure endorphin and keflin [ph],
13 they rise, because they have the expectation of pain
14 relief.

15 DR. WARD: That may be the whole mechanism of
16 sucrose, also, if there is an opioid receptor component to
17 sucrose.

18 Fascinating and helpful discussions, I think.
19 Any other comments?

20 Dr. Buckman, I apologize. We sort of cruised
21 ahead here. Do you want to make some comments?

22 DR. BUCKMAN: I think if everything from the

1 discussion has been supportive, we have no further
2 comments. We really felt strongly about getting this
3 written request out there into the foundation, and we
4 would like to see these studies accomplished.

5 **Adjournment**

6 DR. WARD: All right. We have beaten the clock
7 again this afternoon. I think it has been a very
8 productive discussion. First, you have done your
9 homework, which we all truly appreciate. There has been a
10 lot of information to go through, and I think it has
11 really helped illuminate the discussion.

12 So we will resume in the morning at 8:00. Thank
13 you very much.

14 Oh, yes, turn these in or leave them there and
15 we will pick them up.

16 [Whereupon, at 3:15 p.m., the meeting was
17 recessed, to reconvene at 8:00 a.m., the following day.]

18 + + +

CERTIFICATION

This is to certify that the attached proceedings

BEFORE THE: NICHD Best Pharmaceuticals
 for Children Act (BPCA)

HELD: October 25, 2004

were convened as herein appears, and that this is the
official transcript thereof for the file of the Department
or Commission.

DEBRA DERR, Court Reporter